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PANCREATITIS

AN ANATOMIC STUDY OF THE PANCREATIC AND EXTRAHEPATIC BILIARY SYSTEMS

WILLIAM F. RIENHOFF JR., M.D.

BALTIMORE

AND

KENNETH L. PICKRELL, M.D.

DURHAM, N. C.

In the majority of diseases of the upper part of the abdomen, the symptoms are sufficiently well defined to permit a definite diagnosis. Probably the most prominent exception in this respect is the pancreas. At the same time, this organ is often involved in pathologic conditions of the surrounding viscera and even in diseases of more remote regions. The problem of pancreatitis is the old problem of abdominal surgery and, since a direct attack on the pancreas is as yet fraught with so much danger, a proper consideration of prepancreatic and peripancreatic disease, together with the etiologic factors as forerunners of acute and of chronic pancreatitis, becomes of vital importance. There is ample evidence [1] to prove that cholecystitis and acute and chronic pancreatitis coexist in a large percentage of cases, but the cause of such coexistence is still obscure.

Where does the provocative agent come from? Among the many explanations of the cause of pancreatitis, the one attributing the condition to a reflux of bile into the pancreatic duct seemed the most plausible to the greatest number of clinicians until Rich and Duff,[2] seeking the cause of acute hemorrhagic pancreatitis in cases in which there was no ampulla of Vater, conclusively demonstrated that in some cases acute hemorrhagic pancreatitis is due to metaplasia of the epithelium of the duct with associated dilatation of the duct and acinar rupture behind the obstructing metaplasia. And yet a cursory review of the literature on acute pancreatitis is sufficient to impress on one that there is still a striking lack of agreement among investigators concerning the cause. In order to understand the problem, it is necessary to assemble all the information available and then to weigh the interrelations of these facts.

HISTORICAL ASPECTS

The earlier anatomists, among them Galen and Vesalius, gave little thought to the pancreas, believing that it acted as a cushion to support and protect the stomach and adjacent structures; and it was not until 1641 that Moritz Hoffmann first discovered the duct of the pancreas while working on a rooster and showed his findings to Wirsung, who one year later dissected the duct in the pancreas of a human body, thus making possible a proper interpretation of its physiology. In a letter to Jean Riolan Jr., professor of anatomy in Paris, Wirsung gave the world the first account of his important discovery. Wirsung had a drainage of the duct reproduced on a copper plate,[3] from which but few copies were struck off. According to Choulant,[4] only two copies are known to be preserved. Schirmer [5] saw one in the University of Strasbourg and had a photolithographic reproduction of it made.

To G. Dominici Santorini [6] belongs the credit for the first description of the accessory pancreatic duct and for the first representation ap-

From the Department of Surgery, Johns Hopkins University School of Medicine and Hospital, and the Department of Surgery, Duke University School of Medicine and Hospital.

1. Edgahl, A.: A Review of One Hundred and Five Reported Cases of Acute Hemorrhagic Pancreatitis, with Special Reference to Etiology, with a Report of Two Cases, Bull. Johns Hopkins Hosp. **18**:130, 1907. Mayo, W. J.: The Surgical Treatment of Pancreatitis, Surg., Gynec. & Obst. **7**:607, 1908.

2. Rich, A. R., and Duff, G. L.: Experimental and Pathological Studies on the Pathogenesis of Acute Hemorrhagic Pancreatitis, Bull. Johns Hopkins Hosp. **58**:137, 1936.

3. Wirsung, G.: Figura ductus cujusdam cum multiplicibus suis ramulis noviter in pancreate observ, Padoue, 1642.

4. Choulant, J. B.: Geschichte und Bibliographie der anatomische Abbildungen, Leipzig, R. Weigel, 1852.

5. Schirmer, A. M.: Beitrag zur Geschichte und Anatomie des Pankreas, Inaug. Dissert., Basel, L. Reinhardt, 1893.

6. Santorini, G. D.: Anatomici summi septemdecim tabulae, Parmae, ex regia typog., 1775, p. 150, tabulae XII and XIII.

proximating accuracy of the arrangement of the ducts in the adult human pancreas. He called attention to the existence of the two papillae in the duodenal mucosa and illustrated them in his published work. But it was Bidloo [7] who first noted the papilla common to both the bile and the pancreatic duct. In this connection, also, Regner de Graaf [8] previously had reported that, contrary to what had been the prevailing opinion, the pancreas might present two or even three ducts.

A complete list of the workers on this particular problem in connection with the pancreas is lengthy [9]; it includes such names as Vesling, Bartholinus, Swalve, Blasius, von Muralt, Henle, Sappey, Charpy, Helly, Verneuil, Hamburger, Huschke, Cruveilhier and Christianus Ludovicus Welsch. Now that the identity of the ducts had been established, investigators, such as Albrecht von Haller, Tiedemann and Bécourt, began to report anomalous conditions [10] of these passages. Meckel's was a significant statement [11] in explanation of the causative factors involved in the production of the numerous anomalous conditions, i. e., that atrophy of the duodenal end of the accessory duct was the developmental rule. In 1846, Claude Bernard [12] again revived interest in the accessory pancreatic duct, but it was not until 1896, when Langerhans [13] published his dissertation describing its minute anatomy, that a proper physiologic interpretation of the pancreas was made possible.

EMBRYOLOGY

In order to more clearly understand the arrangement of the ducts and their accessory features in the adult, it is necessary to start at the very beginning, with the embryology of the organ, which has engaged the attention of many workers.[14]

The pancreas arises, as do all the organs of the gastrointestinal tract, as an outpouching or outbudding from the wall of the primitive gut, like a glove finger pushing out from inside the wall. The hollow of this bud, or finger, forms the final duct; the cells at the end grow and develop into the secreting cells of the acini. The pancreas develops from the duodenum at the level of the hepatic diverticulum,[15] from which the cephalic portion of the head and all the neck,

7. Bidloo, G.: Anatomia humani corporis, Amstelodami, vid. J. à Someren, 1685.

8. de Graaf, R.: Tractatus anatomico-medicus de succi pancreatici natura et usu, Lugd. Bat., ex off. Hackiana, 1671.

9. (*a*) Veslingius, J.: Syntagma anatomicum, Patavii, typ. P. Frambotti, 1647. (*b*) Bartholinus, T.: Anatomia, Dordrecht, J. Soury, 1656; Anatomy, London, Nicholas Culpeper and Abdiah Bole, 1668. (*c*) Swalve, B.: Pancreas pancrene, Amstelodami, E. Weyerstraten, 1667. (*d*) Blasius, G.: Zootomiae seu anatomes variorum animalium pars prima, Amstelodami, A. Wolfgang, 1677. (*e*) von Muralt, J.: Vade mecum anatomicum, Tiguri, typ. D. Gessneri, 1677. (*f*) Henle, F. G. J.: Handbuch der systematischen Anatomie des Menschen, Braunschweig, F. Vieweg u. Sohn, 1873. (*g*) Sappey, M. P. C.: Traité d'anatomie descriptive, Paris, V.-A. Delahaye & Cie, 1889, vol. 4, p. 272. (*h*) Charpy, A.: Variétés et anomalies des canaux pancréatiques, J. de l'anat. et physiol. **34**:720, 1898. (*i*) Helly, K. K.: Beiträge zur Anatomie des Pankreas und seiner Ausführungsgänge, Arch. f. mikr. Anat. **52**:773, 1898; Zur Pankreasentwicklung der Säugethiere, ibid. **57**:271, 1900-1901; Zur Frage primären Lagebeziehungen bei der Pankreaslagen des Menschen, ibid. **66**:631, 1904. (*j*) Hamburger, O.: Zur Entwickelung der Bauchspeichel drüse des Menschen, Anat. Anz. **7**:707, 1892. (*k*) Huschke, E.: Traité de splenchnologie et des organes des sens, translated from the German by A. J. L. Jourdan, Paris, J.-B. Baillière, 1845. (*l*) Cruveilhier, J.: Traité d'anatomie descriptive, ed. 4, Paris, P. Asselin, 1861. (*m*) Welsch, C. L.: Tabulae anatomicae, Lipsiae, H. C. Cröker, 1697.

10. (*a*) Haller, A.: Elementa physiologiae corporis humani, Berne, 1764-1766, vols. 6-8. (*b*) Tiedemann, F.: Sur les différences que le canal excréteur du pancréas présente dans l'homme et dans les mammifères, J. compl. du dict. d. sc. méd. **4**:330, 1819. (*c*) Tiedemann, F., and Gmelin, L.: Die Verdauung nach Versuchen, Leipzig, K. Groos, 1826.

11. Meckel, J. F.: Handbuch der pathologischen Anatomie, Leipzig, C. H. Reclam, 1812-1816, vol. 3.

12. Bernard, C.: Mémoire sur le pancréas, Paris, J.-B. Baillière, 1856.

13. Langerhans, P.: Beiträge zur mikroskopischen Anatomie der Bauchspeicheldrüse, Berlin, G. Lang, 1869.

14. (*a*) His, W.: Anatomie menschlicher Embryonen, Leipzig, F. C. W. Vogel, 1885, vol. 3. (*b*) Phisalix, C.: Étude d'un embryon humain de 10 mm., Arch. de zool. exper. et gén. **6**:47, 1888. (*c*) Zimmerman, J.: Rekonstructionen eines menschlichen Embryos von 7 mm., (supp.) Anat. Anz. **4**:139, 1889. (*d*) Felix, W.: Zur Leber und Pancreasentwickelung, Arch. f. Anat. u. Entwcklngsgesch., 1892, p. 281. (*e*) Janösík, J.: Histologie a mikroskopická anatomie, v Praze, Bursík & Kohout, 1892; Le pancréas et la rate, Bibliog. anat., 1895, p. 68. (*f*) Jankelowitz, A.: Ein junger menschlicher Embryo und die Entwicklung des Pankreas bei demselben, Arch. f. mikr. Anat. **46**:702, 1895; Zur Entwicklung der Bauchspeicheldrüse, Inaug. Dissert., Berlin, G. Schade, 1895. (*g*) Swaen, A.: Recherches sur le développement du foie, du tube digestif, de l'arrière—cavité du péritoine et du mésentère, J. de l'anat. et physiol. **32**:1, 1896; **33**:32, 222 and 525, 1897 (pl. I-II, VII and XVI-XVII). (*h*) Volker, O.: Ueber die Verlagerung des dorsalen Pankreas beim Menschen, Arch. f. mikr. Anat. **62**:727, 1903; Beiträge zur Entwickelung des Pankreas bei den Amnioten, ibid. **59**:62, 1902. (*i*) Kollman, J.: Handatlas der Entwickelungsgeschichte des Menschen, Jena, G. Fischer, 1897, vol. 2. (*j*) Ingalls, N. W.: Beschreibung eines menschlichen Embryos von 4.9 mm., Arch. f. mikr. Anat. u. Entwcklngsgesch. **70**:506, 1907.

15. Thyng, F. W.: Models of the Pancreas in Embryos of the Pig, Rabbit, Cat, and Man, Am. J. Anat. **7**:489, 1908.

the body and the tail of the pancreas develop. Diverse views are still entertained concerning the duplicity of the ventral anlage, which arises in close proximity to the common duct. Some maintain that the bud is single, while others hold that at the beginning it consists of two lateral halves which subsequently fuse or one of which disappears, perhaps forming the source of aberrant pancreatic tissue often found along the wall of the gut. As development progresses, the ducts unite, as shown in figure 1 *B*, the duct of the dorsal anlage undergoing a certain degree of atrophy at its duodenal end [11] to produce the adult arrangement, shown in figure 2*A*.

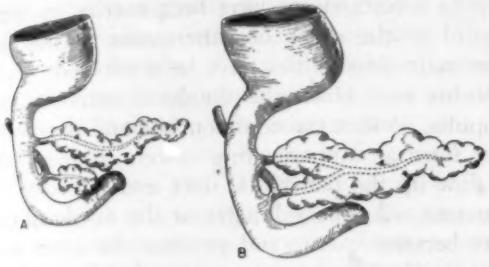

Fig. 1.—Pancreas of a human embryo: *A*, fifth week; *B*, seventh week.

The close relationship between this portion of the pancreas and the common duct is thereby explained. Depending on the eccentricities of development, the relationship will vary somewhat; the common duct may be entirely surrounded by pancreatic tissue; pancreatic tissue may occur even in the wall of the duct itself.

This relation of the exact point of origin of the persisting ventral bud to the common duct determines the final relation of the main pancreatic duct to the common duct. If the pancreatic anlage has grown out from the wall of the common duct itself, the final pancreatic duct will open into the ampulla of the common duct. If the pancreatic anlage has grown out from the wall of the common duct itself, the final pancreatic duct will open into the ampulla of the common duct. If the pancreatic anlage has grown out from the wall of the gut in close proximity to the common duct, the openings of the two ducts will be in close proximity, yet the pancreatic duct may really open into the intestine and not into the ampulla at all.

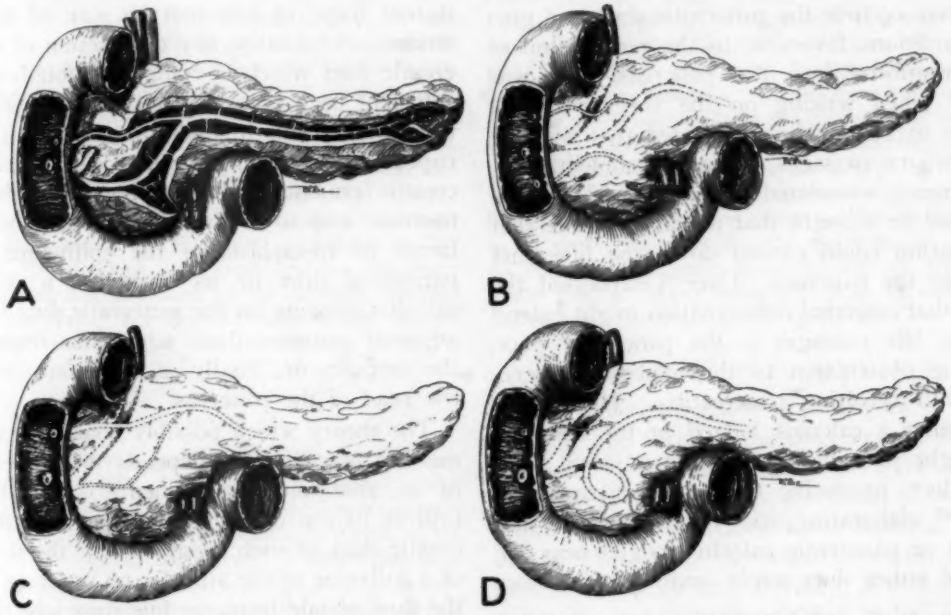

Fig. 2.—*A*, the most constant arrangement of the pancreatic ducts; *B*, specimen with three papillae; *C*, dissected specimen of an adult pancreas showing an embryonic type of duct system in which the accessory duct carries most of the pancreatic secretion; *D*, dissected specimen of an adult pancreas showing an unusual loop configuration of the main pancreatic duct.

The facts seem to be these: Both buds develop by growth in continuity, the dorsal bud giving origin to all of the gland except that portion of the head in close proximity to the common duct and the intestinal wall. The persisting ventral bud grows out but a little way and then fuses with the dorsal bud, giving origin to but a small part of the glandular tissue of the caudal part of the head of the pancreas. In the majority of cases the duct system of this ventral anlage becomes the more important duct system from the point of fusion of the two anlages to the wall of the gut (fig. 1 *B*).

Probably no other region of the body, either in like or in different species, presents more variations than are found in the relation of the component parts of the biliary tract to one another,[16] to the pancreatic duct[17] and to the pancreas and in the relation of all to the duodenum,[18] all of which depend on the relation of the original ventral anlage to the common duct and to the intestinal wall.

ETIOLOGY OF PANCREATITIS

The possibility that gallstones lodged in the ampulla of Vater could cause disease of the pancreas by obstructing the main pancreatic duct was first suggested by Lancereaux,[19] who further mentioned that "a gallstone lodged in the common duct at the level of the diverticulum of Vater may occlude the pancreatic duct and produce conditions favorable to the penetration of micro-organisms into the pancreas." It was Körte,[20] when writing on the surgery of the pancreas in 1898, who first noted that diseases of the biliary passages, especially cholelithiasis, are frequently associated with lesions of the pancreas, and he thought that it was probable that inflammation could extend down the bile duct and enter the pancreas. Oser[21] expressed the opinion that catarrhal inflammation might extend from the bile passages to the pancreatic duct, producing obstruction to the pancreatic secretions, with resulting pancreatitis. He further noticed that a calculus lodged in the common duct might partially occlude the adjacent pancreatic duct, producing the same consequences. Ebstein,[22] elaborating still further, stated that a biliary or pancreatic calculus lodged near the orifice of either duct might occlude both, since the common duct and the pancreatic duct enter the intestine contiguously, at least in some instances.

Since Balser[23] in 1882 first accurately described disseminated fat necrosis, the most extensive investigations have been carried out with regard to the cause of pancreatitis. Thus far, four main possibilities have been evolved: 1. A calculus may block the duodenal orifice of the ampulla, so that the common bile and pancreatic duct form a communicating system, allowing bile to flow up the pancreatic duct and infiltrate the pancreas. 2. The sphincter at the duodenal end may become spastic and produce the same condition. 3. The pancreas may be infected by bacteria reaching it by way of the lymph channels from a diseased gallbladder or from a more distant focus of infection by way of the blood stream. 4. Lastly, any obstruction of the pancreatic duct which is complete enough to cause sufficient back pressure of the pancreatic secretions may result in dilatation of the ducts and rupture of the acini, thereby releasing the pancreatic ferments with resulting hemorrhage, fat necrosis and so forth, whether the obstructing factor be metaplasia of the epithelium of the pancreatic duct or its branches, a pancreatic calculus pressing on the pancreatic duct from the adjacent common duct, a calculus impacted at the ampulla or, finally, a carcinoma involving the head of the pancreas.

The theory which possibly boasts the greatest number of adherents depends on the existence of an anatomic arrangement of the duodenal orifices of the common bile duct and the pancreatic duct of such a nature that the impaction of a gallstone in the ampulla of Vater will direct the flow of bile from the bile duct into the pancreatic duct. Since cholecystitis and acute and chronic pancreatitis coexist in a large percentage of cases,[1] the relationship of the common duct to the pancreatic duct has assumed increased importance. The first thing to be determined in the solution of this problem is the approximate percentage of persons in whom the main pancreatic duct and the common bile duct communicate with the duodenum by a common ampulla.

In order to verify the reported discrepancies concerning the relation of the pancreatic duct to the common duct, 250 human specimens were carefully dissected, special attention being paid in each to the terminal ends of the ducts.

The anatomy of the extrahepatic biliary system shows a great variety of arrangement of its

16. Mann, F. C.; Brimhall, S. D., and Foster, J. P.: The Extrahepatic Biliary Tract in Common Domestic and Laboratory Animals, Anat. Rec. **18**:47, 1920.

17. Mann, F. C.; Foster, J. P., and Brimhall, S. D.: The Relation of the Common Bile Duct to the Pancreatic Duct in Common Domestic and Laboratory Animals, J. Lab. & Clin. Med. **5**:203 (Jan.) 1920.

18. (*a*) Letulle, M., and Nattan-Larrier: Région vatérienne du duodénum et ampoule of Vater, Bull. Soc. anat. de Paris **12**:491, 1898. (*b*) van Balen Blanken, G. C.: Bijdrage tot de kennis der anatomie van pancreas en lymphaatstelsel der primaten, Amsterdam, N. V. Drukkerij "de Nieuwe Tijd," 1912.

19. Lancereaux, E: Traité des maladies du foie et du pancréas, Paris, O. Doin, 1899.

20. Körte, W.: Die chirurgischen Krankheiten und die Verletzungen des Pancreas, Stuttgart, F. Enke, 1899.

21. Oser, L.: Die Erkrankungen des Pankreas, in Nothnagel, C. W. H.: Specielle Pathologie und Therapie, Vienna, A. Hölder, 1898, vol. 17, pt. 2, p. 286.

22. Ebstein, W.: Diabetes Mellitus, Unterleibskoliken und Oedeme in ihren Wechselbeziehungen, Ztschr. f. klin. Med. **40**:191, 1900.

23. Balser, W.: Ueber Fettnekrose, eine zuweilen tödtliche Krankheit des Menschen, Virchows Arch. f. path. Anat. **90**:520, 1882.

component parts; in like manner, a comparison of the relationship between the bile duct and the pancreatic duct reveals great variability. Furthermore, the method by which the bile duct and pancreatic ducts enter the duodenum is exceedingly variable, not only in closely related species but in individuals of the same species. Practically all textbooks of anatomy [24] describe these two ducts as usually uniting to form a common channel at their duodenal extremities.

MATERIAL

The material in this study consisted of both fresh and fixed adult human pancreases obtained from the autopsies of the department of pathology and fixed specimens from this department and also from specimens used in the routine dissecting courses in the department of anatomy of Johns Hopkins School of Medicine. The pancreases were from 150 men and 100 women ranging in age from 19 to 83 years. Death in no instance was caused by a pathologic process localized in either the duodenum or the pancreas.

The entire work on the accessory pancreatic duct was carried out on 100 fresh autopsy specimens, because dissection of the duct after fixation was often difficult and many times the patency of the duct could not be accurately determined. The work on the main pancreatic duct and the common bile duct was carried out on 250 specimens, 100 of which were fresh and the remainder of which were fixed, because of the difficulty encountered in preserving the delicate membranous septum which often separates the duct of Wirsung from the common bile duct.[25]

METHODS

The main pancreatic duct was first located by gross dissection in the middle of the neck of the gland, where the pancreatic tissue overlies the superior mesenteric vessels. Here the duct comes within 2 to 3 mm. of the surface and can readily be followed in either direction.

The accessory duct was most quickly found by following the main pancreatic duct along its ventral surface toward the duodenum. In these anomalous instances in which the duct could not be found by this method or in which there was no apparent communication between the ducts, the second part of the duodenum was opened along its right free border and the position of the minor papilla ascertained. Then, this being used as a guide, the accessory duct was sought for in the glandular tissue cephalad to the level of the papilla. In those instances in which no communication between the main and the accessory duct could be demonstrated even after painstaking dissection, the patency of the accessory duct and the minor papilla was established by inserting a small needle into the main duct and injecting air under minimal pressure while the entire specimen was submerged in water. If no bubbles emerged from the minor papilla, a hypodermic needle was inserted into the accessory duct to establish the patency of its duodenal end. Minimal pressure was used in order to avoid bursting of any natural barrier which might have been present at the blind duodenal end of the accessory duct.

If then no communication could be established, the main duct was injected with methylthionine chloride or eosin after the accessory duct had been ligated where the hypodermic needle had been inserted to test the patency of its duodenal end. Regurgitation of the dye evidenced the presence of a communication between the ducts.

The relation of the main pancreatic duct to the terminal part of the common duct was ascertained by incising the common duct near the entrance of the cystic duct and then opening it to its termination. Likewise, the pancreatic duct was followed from its communication with the accessory duct to its duodenal end, to ascertain what part, if any, it played in the formation of an ampulla. Careful measurements of the distance of the opening from the duodenal end of the bile duct were made with caliper points and recorded.

No attention was given to a study of the intestinal valves. The duodenum was opened along its right free border, and the major and minor papillae were identified in all specimens. Locating the major papilla presented no difficulty; the same, however, was not true of the minor papilla. Many times only after the most careful search could the minor papilla be found.

THE MAIN PANCREATIC DUCT

The main pancreatic duct begins in the tail of the gland through the convergence of several small duct radicles and pursues a more or less tortuous course through the body of the gland, approximating the dorsal and cephalic portions of the gland. In the head, however, the duct inclines caudally and dorsally, forming a wide arc with its convexity to the right, as it approaches the dorsal surface of the head of the gland. Reaching the level of the terminal part of the common duct, it runs horizontally to join with the caudal aspect of the common bile duct to form the major duodenal papilla.

In the 100 specimens studied for this purpose the tributaries of the main pancreatic duct in the body of the gland were observed to join the duct almost invariably at right angles and also to alternate with tributaries of the opposite side in the level at which they joined the duct (fig. 2 *A*). The same arrangement was also present in the radicles of these tributaries, except in the head of the gland, in which this conformity was frequently departed from, both as to the position of the tributaries and as to their angle of junction. In 61 instances there was found a moderately large unpaired trunk, as shown in figure 2 *A*, which drained the small lobe of

24. Gray, H.: Anatomy of the Human Body, edited by W. H. Lewis, ed. 22, Philadelphia, Lea & Febiger, 1930, p. 1191. Morris, H.: Morris' Human Anatomy, edited by C. M. Jackson, ed. 9, Philadelphia, P. Blakiston's Son & Co., 1933, p. 1287. Cunningham, D. J.: Cunningham's Textbook of Anatomy, edited by A. Robinson, ed. 5, New York, William Wood & Company, 1923, p. 1194. Piersol, G. M.: Human Anatomy, edited by G. C. Huber, ed. 9, Philadelphia, J. B. Lippincott Company, 1930, p. 1737.

25. Abeberry Oneto, A.: Anatomía del duodeno y páncreas, Semana méd. **27**:395, 1920.

pancreatic tissue overlying the mesenteric vessels, described in 1732 by Winslow and later called to attention by Charpy. In 1 instance this trunk was found to communicate directly with the duodenum through a third papilla, draining the lobe of Winslow and the entire caudal part of the head of the gland, as shown in figure 2*B*.

The main duct was found to drain the entire tail, body and neck and in 61 instances the dorsal half of the head and the caudal part of the ventral half as well, restricting the accessory duct to the draining of only that part of the head in the immediate proximity of the minor papilla. In 7 instances the accessory duct drained the entire cephalic half of the head, and in 4 instances the main duct was restricted to draining the dorsal and the caudal part of the head, the embryonic arrangement of the ducts, as represented in figure 2 *C*.

In 2 instances another rather unusual arrangement of the ducts was found, similar to that in the 3 specimens found by Baldwin [26] and represented in figure 2 *D*. In these instances the main duct formed a complete loop before joining the common duct. The accessory duct occupied its usual position and joined the main duct before the beginning of the loop. In no instance was the main duct duplicated in the body of the pancreas, as described by Bernard,[12] or the spiral disposition of the pancreatic duct, described by Hyrtl [27] in his "Die Corrosions-Anatomie und ihre Ergebnisse."

THE ACCESSORY PANCREATIC DUCT

The accessory duct was present in all 100 specimens dissected for this purpose. In only 89 instances could a communication be found between the ducts after air, dyes or both had been injected and followed by minute dissections.

From the figures in table 1, the main and the accessory duct are shown to communicate within the gland in about 85 per cent of the specimens. Invariably the accessory duct lay on a plane ventral to that of the main duct and communicated with it in the head near the neck of the gland. In 51 instances the accessory duct described two curves as it proceeded toward the duodenum. The first, at the duct end, had its concavity cephalad, while the shorter one, at the duodenal end, had its concavity caudad, as shown in figure 2 *A*. In 6 instances these curvatures were reversed, and in 24 instances the duct formed a wide curve, at times descending caudal to the main duct. In no instance, however, was it ever found wholly caudal to the main duct. In 4 instances the embryonic arrangement of the ducts was found, i. e., the accessory duct was larger than the main duct and drained the entire cephalic half of the head, together with the neck, the body and the tail, while the main duct was limited entirely to the caudal part of the head, as shown in figure 2 *C*. Regardless of the curvature followed or the arrangement of the ducts, in 67 instances the accessory duct was restricted to the ventral and cephalic portion of the head. This finding is in accord with those of the work of Charpy [9b] and also the later work of Baldwin,[26] who found that the accessory duct was restricted to the cephalic and ventral aspect in 45 of 66 specimens. Opie, however, stated the belief that the accessory duct drained the "anterior and lower part of the head." And it is a curious fact, in spite of the evidence to the contrary, that most textbooks and atlases of anatomy illustrate the caudal part being drained by the accessory duct.

TABLE 1.—*Interglandular Communication of the Pancreatic Ducts*

	Junction	No Junction
Opie	90	10
Duval	?	1
Helly	48	2
Charpy	28	2
Schirmer	65	34
Verneuil	20	0
Baldwin	66	10
Rienhoff and Pickrell	89	11
Total	406	70
Per cent	85	15

If one excludes the 11 instances in which no communication could be found between the main and the accessory duct and the 4 instances in which the duct system was reversed, the accessory duct being larger than the main duct—in which naturally the accessory duct approached the duodenum with augmenting caliber—there are 73 of 85 specimens, about 86 per cent, in which there was a normal duct arrangement and the duct approached the duodenum with diminishing caliber. These facts are in accord with Meckel's hypothesis [11] that the pancreatic ducts in the fetus are of equal caliber but that as development progresses the accessory duct atrophies somewhat at its duodenal end. This fact was also noted by Bernard [12] and verified by

26. Baldwin, W. M.: The Pancreatic Ducts in Man, Together with a Study of the Microscopical Structure of the Minor Duodenal Papilla, Anat. Rec. **5**:197, 1911; The Ductus Pancreaticus Accessorius in Man, ibid. **1**: 66, 1907.

27. Hyrtl, J.: Die Corrosions-Anatomie und ihre Ergebnisse, Vienna, W. Braumüller, 1873; Handbuch der topographischen Anatomie und ihrer praktisch medicinischchirurgischen Anwendungen, ibid., 1865.

Schieffer [28] on human fetuses and still later by Baldwin,[26] who made microscopic preparations of the terminal part of the accessory duct and the minor papilla.

The average diameter of the undistended duct in the 85 specimens with a normal duct arrangement at its point of perforation of the duodenal wall was 1.6 mm. The size of the duct, however, was no criterion of its patency, for only 62, about 73 per cent, were found to be patent by use of the injection method, whereby either air or dyes or both were injected under minimal pressure in order to avoid breaking through any natural barrier which might have been present. This gives, then, 23 specimens, about 27 per cent, which did not communicate with the duodenum. This is considerably higher than Helly's 20 per cent [91] and Baldwin's 10 per cent of 50 specimens,[26] in both groups of which the terminal part of the accessory duct was examined microscopically. These results, however, are in accord with those obtained by use of the injection technic (see table 2).

TABLE 2.—*Patency of the Accessory Duct*

	Injection Method	
	Patent	Closed
Schirmer	85	19
Charpy	9	21
Opie	79	21
Verneuil	20	0
Sappey	16	1
Rienhoff and Pickrell	62	23
Total	271	85
Per cent	76	24

In the 4 instances in which the duct system was reversed and the 11 instances in which no intraglandular communication of the ducts could be demonstrated, the accessory duct approached the duodenum with increasing caliber and with a patent papilla, leaving 23 per cent of all specimens in which the papilla was closed, regardless of the duct arrangement. Of practical interest, however, is the fact that in 11 per cent the ducts did not communicate and in 23 per cent the papilla was closed, making a total of 34 per cent in which fluid could not pass from the main duct to the duodenum by way of the accessory duct.

Complete absence of the accessory duct seems to be a rare anomaly, since it occurs in less than 1 per cent of specimens examined (table 3). Inversion of the ducts occurs in about 7 per cent (table 4).

28. Schieffer, J.: Du pancreas dans la série animale, Thesis, Montpellier, 1884.

RELATION OF THE AMPULLA OF VATER TO PANCREATITIS

Bécourt,[29] Bernard [12] and Laguesse [30] each mentioned 1 specimen in which the main pancreatic duct opened into the duodenum apart from the orifice of the bile duct. Schirmer [5] found 22 specimens, about 47 per cent, among 47 investigated in which a mucosal septum separated the orifice in such a manner that a true ampulla did not exist. Practically all textbooks of anatomy [24] describe the ducts as usually uniting to form a common channel at their duodenal extremities. Sappey [95] stated that this arrangement is the one which is observed in the great

TABLE 3.—*The Accessory Duct*

	Present	Absent
Schirmer	101	3
Charpy	29	1
Helly	50	0
Verneuil	20	0
Santorini	?	0
Bernard	?	0
Hamburger	50+	0
Sappey	17	0
Opie	100	0
Baldwin	76	0
Rienhoff and Pickrell	100	0
Total	543	4
Per cent		0.737

TABLE 4.—*Inversion of Ducts*

	Specimens Examined	Inversion of Ducts
Schirmer	104	4
Charpy	30	3
Bernard	?	1
Morel and Duval	?	1
Opie	100	11
Bimar	?	1
Moyse	?	1
Baldwin	76	3
Rienhoff and Pickrell	100	4
Total	410	29
Per cent		6.61

majority of cases. One of few exceptions to this view is found in the frequently cited work of Letulle and Nattan-Larrier,[18a] who found that a common channel occurred in only 8, about 38 per cent, of 21 specimens.

Schirmer [5] mentioned 11 specimens in his series of 47 in which the pancreatic duct opened into the bile duct and 14 specimens in the same series in which the bile duct opened into the pancreatic duct. Verneuil [31] seemed to believe

29. Bécourt, P. J. G.: Recherches sur le pancréas, Strasbourgh, F. G. Levrault, 1830.

30. Laguesse, E.: Sur l'existence de nouveaux bourgeons pancreatiques accessoires tardifs, Compt. rend. Soc. de biol. **2**:602, 1895.

31. Verneuil, A.: Mémoire sur quelques points de l'anatomie du pancréas, Gaz. méd. de Paris **6**:384 and 398, 1851; reprint ed., Paris, E. Thunot & Cie, 1851.

that usually the pancreatic duct received the bile duct and that, accordingly, the ampulla of the papilla belonged to the pancreatic duct. Apparently Opie [32] was of the same opinion, for he wrote the following comment concerning the examination of his 100 specimens: "The common bile duct always joined the duct of Wirsung."

Occasionally the pancreatic duct is totally absent. Helly,[91] Charpy [9h] and Cruveilhier [91] each mentioned 1 such instance, while Schirmer [5] mentioned 4. Baldwin [26] found 1 specimen in which the main duct was occluded at its duodenal end. And occasionally the common bile duct opens into the duodenum in company with the accessory duct. Schirmer [5] mentioned 5 such instances.

Through the pioneer work of Opie [33] and many subsequent investigators, sufficient reliable evidence has been accumulated to warrant one in suspecting that a reflux of bile up the main pancreatic duct or the anatomic condition which would permit the conversion of the bile duct and pancreatic duct into a communicating system after the impaction of a calculus in the terminal part of the common duct or the ampulla of Vater is the cause of acute hemorrhagic pancreatitis in at least some of the reported cases.

Opie,[32] after examining 100 specimens, found an ampulla in each of 38 specimens, whose measurements varied from "less than 1 mm. to 11 mm." In only 30 specimens did this measurement equal or exceed 5 mm. It is a question whether a common channel should be considered present if the system of the two ducts extends within less than 2 mm. of the summit of the papilla.

Opie [34] pointed out that the presence of a common channel does not necessarily mean that the common duct and the pancreatic duct can be converted into a freely communicating system by an impacted biliary calculus. He stated that in order for this to take place "it is necessary that the diverticulum of Vater be capacious, with a length at least greater than the length of its duodenal orifice." And he found that in 21 of his 100 specimens the diameter of the orifice was equal to or greater than the length of the diverticulum. He concluded, therefore, that in these 21 specimens it was impossible that a calculus, if it were assumed to be approximately spherical and lodged in the orifice, could only partially occlude the cavity. He [35] likewise asserted that ligation of both pancreatic ducts would cause hemorrhagic pancreatitis, and he reported a case in which calculi in the common duct near the ampulla caused obstruction, while bile had not entered the main pancreatic duct and the duct was not dilated. He collected reports of 7 similar cases from the literature and concluded, "The lodgment of a stone near the orifice of the common bile duct, where it may at the same time compress or occlude the pancreatic duct, is not uncommonly the cause of pancreatic lesions and disseminated fat necrosis." Moynihan [36] expressed the same opinion, for he wrote:

> The actual size of the diverticulum and of its opening on the surface of the duodenum are of great importance from a surgical standpoint, for if the diameter of the opening, for example, be 3 mm., and a calculus 4 mm. in diameter reaches the ampulla from the common duct, it may block the duodenal orifice, being unable to pass, and will, therefore, convert the common bile duct and pancreatic duct into a common closed channel.

By carefully measuring the ampulla, Opie was the first to attempt a solution of this question, and since then the most extensive investigations have been carried out with regard to the cause of pancreatitis, most of which have been based on Opie's work or methods of investigation.

More recently, Ruge,[37] Baldwin,[26] Belou,[38] Sweet,[39] Judd,[40] Mann and Giordano [41] and Cameron and Noble [42] have investigated this question, mainly from an anatomic point of view, while Dragstedt [43] and Rich and Duff [2] have investigated it mainly from the pathogenic aspect. Ruge found a common channel in 32, about 75 per cent, of 43 cadavers examined. Baldwin, in a study of the anatomy of the pancreas, found

32. Opie, E. L.: The Anatomy of the Pancreas, Bull. Johns Hopkins Hosp. **14**:230, 1903.

33. Opie, E. L.: The Etiology of Acute Hemorrhagic Pancreatitis, Bull. Johns Hopkins Hosp. **12**:182, 1901.

34. Opie, E. L.: Diseases of the Pancreas, ed. 2, Philadelphia, J. B. Lippincott Company, 1910, p. 15.

35. Opie, E. L.: The Relation of Cholelithiasis to Disease of the Pancreas and to Fat Necrosis, Am. J. M. Sc. **121**:27, 1901.

36. Moynihan, B. G. A.: Gallstones and Their Surgical Treatment, Philadelphia, W. B. Saunders & Co., 1904, p. 27.

37. Ruge, E.: Beiträge zür chirurgischen Anatomie der grossen Gallenwege, Arch. f. klin. Chir. **87**:47, 1908.

38. Belou, P.: Anatomia de los conductos biliares y de la arteria cistica, Buenos Aires, Imp. "Oceana," 1915.

39. Sweet, J. E.: Surgery of the Pancreas, Internat. Clin. **4**:293, 1915.

40. Judd, E. S.: Relation of the Liver and the Pancreas to Infection of the Gallbladder, J. A. M. A. **77**:197 (July 16) 1921.

41. Mann, F. C., and Giordano, A. S.: The Bile Factor in Pancreatitis, Arch. Surg. **6**:1 (Jan.) 1923.

42. Cameron, A. L., and Noble, J. F.: Reflux of Bile up the Duct of Wirsung Caused by an Impacted Biliary Calculus, J. A. M. A. **82**:1410 (May 3) 1924.

43. Dragstedt, L. R.; Haymond, H. E., and Ellis, J. C.: Pathogenesis of Acute Pancreatitis (Acute Pancreatic Necrosis), Arch. Surg. **28**:232 (Feb.) 1934.

that in 20 of 90, 22 per cent, specimens, the ampulla of Vater was absent and the ducts separated by a distinct septum. In 13 per cent, the distance from the orifice of the ampulla to the septum was 2 mm., and in 1 specimen the duct of Wirsung was reduced to a fibrous cord. No detailed measurements of the remaining specimens were given, except that the average distance from the apex of the ampulla to the septum was 4.8 mm.

Bélou, while making a special study of the biliary tract, investigated the relation of the duct of Wirsung to the common bile duct in 50 specimens and found that in 54 per cent the two opened into the duodenum, either separately or at the apex of the ampulla of Vater; in 30 per cent the duct of Wirsung opened from 1 to 2 mm. from the apex, while for the remaining 26 per cent measurements were lacking.

In Osler's series [44] of 100 specimens, in only 32 was the diverticulum of Vater of such size that a small calculus might occlude the orifice without completely filling it and obstructing one or both ducts entering it. Judd [40] studied 170 necropsy specimens for the purpose of determining the percentage of instances in which the anatomic arrangement was such that it would be possible to convert the two ducts into one continuous passageway. This was a possibility in only 4.5 per cent. He concluded that only very exceptionally is there an anatomic arrangement whereby the ducts can be converted either by a stone or by the action of a sphincter, into a continuous passageway permitting bile to flow from the common duct into the pancreatic duct.

Mann and Giordano [41] examined formaldehyde-fixed specimens obtained from 200 consecutive autopsies. Their technic consisted in simple dissection and measurement of the diameter of the ampulla and its duodenal orifice. In 90 specimens, 45 per cent, the ducts were contiguous and opened from 1 to 2 mm. from the apex of the papilla. In 28 specimens, 14 per cent, the length of the ampulla was 3 mm., while in only 7 specimens, 3.5 per cent, did it equal or exceed 5 mm. Since the average diameter of the ampulla was 2.5 to 3.5 mm. they reasoned that the common bile duct and the pancreatic duct could be converted into a continuous channel only by a blockage of the exit in the specimens in which the length of the ampulla was greater than the diameter of its duodenal orifice, i. e., in 7 instances, or 3.5 per cent. They called attention to the fact, previously noted, that the dimensions of the ampulla and the ducts entering it are often such that a calculus which would become impacted would obstruct both ducts and would not convert them into a continuous channel.

Cameron and Noble [42] resorted to another method of investigation, which consisted in artificially impacting a carefully selected biliary calculus in the ampulla of Vater of a necropsy specimen by stripping it down the common duct and then determining whether a reflux occurred by forcing water or bile down the common duct under a pressure of 100 mm. or less and observing whether it escaped by way of the duct of Wirsung. To insure that the calculus was firmly lodged in the ampulla, a pressure of 1,800 mm. of water was brought to bear on the system. Irregular calculi were used most often, and not infrequently a part of the calculus protruded into the duodenum. Casts of these specimens in which a reflux occurred were obtained by pouring Wood's metal at 180 C. into the common duct, which ran up the duct of Wirsung and hardened immediately. When the cast was exposed, the points between which to measure were usually well defined.

After 100 specimens had been examined, an ampulla was found in 74 instances. In 8 of these, the size of the duodenal orifice was so great and the length of the ampulla so short that it was impossible to convert the two ducts into a common system by means of an impacted calculus. In the remaining 66, this was possible. They concluded, therefore, that in 66 per cent of 100 specimens it was anatomically possible for the common duct and the pancreatic duct to be converted into a single communicating system by an impacted biliary calculus. This figure contrasts sharply with Judd's 4.5 per cent in 170 specimens and Mann and Giordan's 3.5 per cent in 200 specimens.

STUDIES ON THE AMPULLA OF VATER

The foregoing review affords evidence that a considerable difference exists between the results of various observers. Because a more detailed study of the exact length of the ampulla of Vater is necessary, especially with reference to the percentage frequency of its variations, and in order to verify the reported discrepancies concerning the relation of the main pancreatic duct and the common bile duct, this study was undertaken.

The specimens consisted of 250 adult human pancreases obtained from both men and women ranging in age from 19 years to 83 years. Death in no instance was due to a pathologic process localized either in the pancreas or in the duodenum. Dissection was carried out in the fresh in 100 of the specimens, as previously outlined, and careful measurements were recorded with

44. Osler, W.: Modern Medicine, Philadelphia, Lea & Febiger, 1908, vol. 5, p. 637.

caliper points of the distance from the pancreatic duct, the dividing septum, to the apex of the papilla. These specimens were soon fixed in 4 per cent solution of formaldehyde in order to preserve the delicate membranous septum which often separates the duct of Wirsung from the terminal part of the common duct. The shrinkage caused by fixation falls within the limits of error, since sharply defined points between which to measure are not constant. This is particularly true when one is dealing with an obliquely placed, slitlike duodenal orifice in which there is a difference of 1 mm. or more between the short and the long diameter as measured from the margin of the orifice. In these instances, the long diameter was recorded. The average diameter of the papilla in 250 specimens was found to be 3 mm., with limits of 1.5 mm. and 4.5 mm.

These observations are recorded in table 5 and compared with those of Mann and Diordano and Cameron and Noble. In 73 of 250 specimens, about 29 per cent, there could be found no junction of the pancreatic and the bile duct, each entering the duodenum contiguously or at separate points, as shown in figure 3 *A*. In 92 specimens, 37 per cent, the two ducts were contiguous, the dividing septum terminating 1 to 2 mm. from the apex, forming a common orifice for the bile and pancreatic duct, as shown in figure 3 *B*. In this group a true ampulla was not considered present, since it is a question whether a common channel should be considered present in specimens in which the septum of the two ducts extends within 2 mm. of the summit of the papilla. In 81 instances, 32 per cent, the ducts emptied into a common ampulla from 3 to 14 mm. from the apex of the duodenal orifice (fig. 3 *C*). In 4 of these specimens the length of the diverticulum exceeded 10 mm., as shown in figure 3 *D*. In 4 instances the pancreatic duct was reduced almost to a fibrous cord and doubtless had little if any function during life, while the accessory duct drained the entire gland.

If one subscribes to the same reasoning as outlined by Opie and employed by Mann and Giordano, the common duct and the pancreatic duct could be converted into a communicating system by a blockage of the exit of the ampulla only in group 3, in which the ducts communicated by a definite diverticulum, and in this group the process could be brought about only in the specimens in which the pancreatic duct empties into the ampulla at a greater distance from the exit than the diameter of the common opening. The average diameter of the ampulla was found to be 3 mm. Of the 32 per cent of the specimens in which an ampulla was present, in 34 specimens, 14 per cent, the opening of the pancreatic duct was 3 mm. from the apex of the papilla.

TABLE 5.—*Relation of the Main Pancreatic Duct to the Common Bile Duct*

Author	Group	Location of Opening of Pancreatic Duct	Specimens		Distance from Apex of Ampulla to Dividing Septum, Mm.											
			Number	Per Cent	3	4	5	6	7	8	9	10	11	12	13	14
Mann and Giorgano	1	Separately into duodenum	62	21												
	2	2 mm. from apex of ampulla	90	45												
	3	3 to 10 mm. from apex	40	20	28	6	3	0	1	2	0	1+				
	4	Duct absent or closed	8	4												
		Total	200	100												
Cameron and Noble	1	Separately into duodenum	26	26												
	2	2 mm. from apex of ampulla	12	12												
	3	5 to 13 mm. from apex	48	48	..	..	8	12	13	6	2	3	2	1	1	
	4	No data	14	14												
		Total	100	100												
Rienhoff and Pickrell	1	Separately into duodenum	73	29												
	2	2 mm. from apex of ampulla	92	37												
	3	3 to 14 mm. from apex	81	32	34	17	11	8	3	3	1	0	2	1	0	1
	4	Duct absent or closed	4	2												
		Total	250	100												

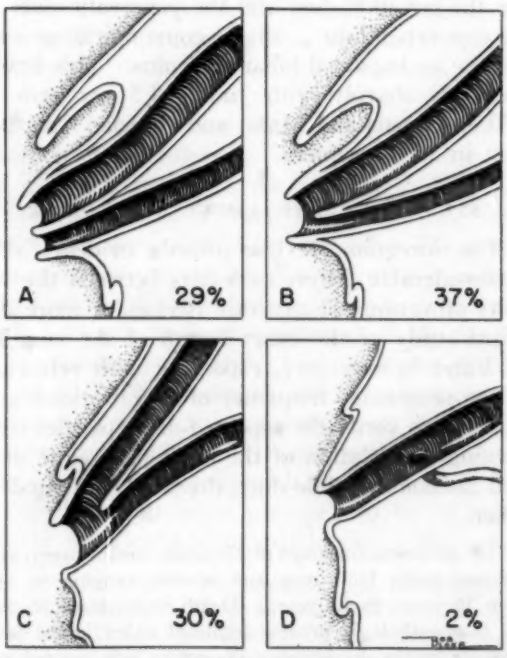

Fig. 3.—Variations of the entrance of the main pancreatic duct into the common duct.

In the majority of instances, then, a calculus must be 4 mm. in diameter before it can cause obstruction, if one assumes that it is approximately spherical. This, however, seems the exception rather than the rule, since irregularly shaped calculi are encountered more frequently than spherical ones. This leaves, then, 47 specimens, about 18 per cent, in which the length of the ampulla exceeded the average diameter of the duodenal orifice and in which a complete block at the papilla by an impacted calculus would convert the ducts into a communicating system. This reasoning, however, is open to several serious objections. In the first place, conclusions formulated from measurements taken between poorly defined points, of differences of 1 mm. or less, seem decidedly inaccurate, since average measurements may never actually occur in a single instance. In the second place, the obstructing calculus was spherical, when irregularly shaped calculi are encountered more frequently, and, as suggested by Cameron and Noble,[42] a considerable part of an irregularly shaped calculus may project through the orifice of the ampulla into the duodenum, while its length may exceed that of the ampulla, and yet a reflux would be possible. It is true, also, that the greatest diameter of an impacted calculus may equal the long diameter of the ampulla in which it is wholly contained, with a communication existing between the ducts owing to the failure of the irregularly shaped calculus to completely fill the ampulla, which itself may be dilated.

Although it is a matter of definition as to whether an ampulla actually exists in those instances in which the septum extends within 2 mm. of the apex of the papilla, in table 6, in which the measurements are given a true ampulla was not considered present in the specimens. From the figures in table 6, we see that an ampulla is present in about 46 per cent, had the measurements been included in each investigator's report. For example, Cameron and Noble made no mention of the ampullae less than 5 mm., while in Opie's series of 100 specimens, in only 30 did this measurement equal or exceed 5 mm. Oser found only 32 of 100 specimens in which the diverticulum was of such size that a small calculus might occlude the orifice without completely filling it and thus obstruct both ducts. Our findings and the correlation of the greater part of the work done on this particular phase of the problem to the present time lead us to believe that the main pancreatic duct enters the duodenum apart from the common bile duct in 25 to 30 per cent of all cases and that a true ampulla is present in only 30 to 40 per cent.

TABLE 6.—*The Ampulla of Vater*

	Ducts Join to Form Ampulla	No Junction	Specimens Examined
Bécourt	?	1	?
Bernard	?	1	?
Laguesse	?	1	?
Schirmer	25	22	47
Letulle	8	13	21
Opie	89	11	100
Ruge	32	11	43
Baldwin	56	34	90
Belou	8	42	50
Mann and Giordano	40	160	200
Cameron and Noble	74	26	100
Rienhoff and Pickrell	81	169	250
Total	413	491	901
Per cent	46	53	

THE RELATION OF THE SPHINCTER OF ODDI TO PANCREATITIS

Although Glisson [45] expressed the opinion that a sphincter existed at the end of the common bile duct, it was first described by Gage,[46] who studied the sphincter in the cat and found sphincters around the pancreatic and common bile ducts and one group of muscle fibers passing around both ducts. Oddi,[47] employing many species of animals, made an extensive comparative anatomic and physiologic study of the sphincter; but, aside from assigning a special sphincter to the duct of Wirsung, he did not study especially the relation of the sphincter of the common bile duct to the pancreatic duct. Somewhat later, Hendrickson [48] studied the sphincter in man, in the dog and in the rabbit. His specimens show muscle fibers surrounding both the common bile and the pancreatic duct.

In the absence of a stone in the ampulla of Vater, it has been suggested that in the instances in which both the bile and pancreatic duct open toghether in the ampulla, a flow of bile from the common duct might be diverted into the pancreatic duct during life by spasm of the sphincter of Oddi.

The possible importance of the sphincter at the duodenal end of the common bile duct was

45. Glisson, quoted by Oddi.[47a]

46. Gage, S. H.: The Ampulla of Vater and the Pancreatic Ducts in the Domestic Cat, Am. Quart. Micr. J. **1**:123 and 169, 1878-1879 (pl. xii-xiv).

47. Oddi, R.: (*a*) D'une disposition à sphincter spéciale de l'ouverture du canal cholédoque, Arch. ital. de biol. **8**:317, 1887; (*b*) Sulla tonicità dello sfintere del coledoco, Arch. per le sc. med. **12**:333, 1888.

48. Hendrickson, W. F.: A Study of the Musculature of the Entire Extrahepatic Biliary System, Bull. Johns Hopkins Hosp. **9**:221, 1898.

suggested by Archibald.[49] He called attention to the fact that bile might be forced into the pancreatic duct as a result of the spasmodic contraction of the sphincter muscle at the end of the duct. In his interesting experiments testing the resistance of the sphincter in the cat, he introduced into the gallbladder infected bile or bile salts and forced these to enter the pancreatic duct by spasm of the sphincter owing to the sudden rise of pressure in the gallbladder from 200 to 700 mm. of water or to the application of hydrochloric acid to the mucous membrane of the duodenum. Necropsy of the animals that lived several hours revealed acute hemorrhagic pancreatitis and multiple focal liver abscesses.

Knowing that removal of the gallbladder cures most patients with cholecystitis and pancreatitis, Judd[40] studied the changes which result from the loss of this organ and found a dilatation of the common duct with a paralysis of the sphincter. This seemed to explain why removal of the gallbladder relieved the inflammation in the pancreas if it was due to a reflux of bile, the result of a spasmodic contraction of the sphincter; if it was due to an extension of infection from the gallbladder through the lymphatics, then removal of the infected viscus would afford relief.

In order to determine whether it would be possible for the sphincter to convert the common bile duct and pancreatic duct into a continuous channel, Judd examined the sphincter in four species of animals in which the two ducts enter the duodenum together; the dog, the cat, the monkey and man. His examination showed clearly that in almost all instances the muscle fibers are intimately connected with both ducts, so that a contraction of the sphincter would simultaneously close the two ducts and would not convert them into a continuous channel. This was first beautifully shown by Hendrickson[48] with macerated specimens. If Archibald's theory is correct, the sphincter would have to be placed distal to the entrance of both ducts in the ampulla. Mann and Giordano[41] made serial sections of the sphincter in man and found that the usual position of the muscle fibers constituting the sphincter is proximal to the termination of the common duct. These observations show that the usual position and arrangement of the sphincter in man are such that it would not be possible for a contraction of the sphincter to convert the ducts into a continuous channel, even if they opened into a common ampulla, which in our series was 32 per cent.

Many interesting experiments have shown that the resistance of the sphincter is modified by various conditions: starvation,[50] local irritation of the sphincter[49] and stimulation of the autonomic nervous system. The sphincter is relaxed through the action of the sympathetic system and is thrown into spasm by stimulation of the parasympathetic system. Drugs acting directly on smooth muscle cause spasm increasing the resistance of the sphincter, while drugs which reduce the tonicity of smooth muscle relax the sphincter.[51] The literature is replete with clinical observations regarding the relationship of the sphincter of Oddi to acute pancreatitis,[49] postcholecystectomy syndrome,[52] dyskinesias of the biliary tract[53] and various forms of jaundice.[54] Recent observations by means of injections of iodized poppyseed oil have clearly demonstrated that spasticity of the sphincter of Oddi occurs in man.[55] Doubilet and Colp[56] measured the resistance of the sphincter in 7 patients with a T tube intubation of the common duct. A variation of 125 to 230 mm. of water, with an average of approximately 165 mm. of water for normal,

49. Archibald, E.: Experimental Production of Pancreatitis in Animals as a Result of Resistance of the Common Duct Sphincter, Surg., Gynec. & Obst. **28**:529, 1919. Archibald, E., and Gibbons, E. C.: Tr. Am. S. A. **39**:96, 1921.

50. Cole, W. H.: Relation of Gastric Content to the Physiology of the Common Duct Sphincter, Am. J. Physiol. **72**:39, 1925.

51. Brugsch, T., and Horsters, H.: Cholagoga und Cholagogie, Arch. f. exper. Path. u. Pharmakol. **118**: 267, 1926. Burget, G. E.: The Relation of the Flow of Bile: II. Effect of Eliminating the Sphincter of Oddi, Am. J. Physiol. **79**:130, 1926. Kitakoji, Y.: Studien ueber die Funktionen der Gallenblase und des Oddischen Muskels in Bezug auf die Absonderung der Blasengalle; ueber den Einfluss von Nervengiften auf die Funktionen der Gallenblase und des Oddischen Muskels, Nagoya J. M. Sc. **5**:24-29 (Nov. 20) 1930. Nakashima, K.: Studies on the Mode of Bile Outflow: About Oddi's Sphincter, Regulator of Bile Outflow, Acta scholae med. univ. im Kioto **9**:357, 1927. Shi, K.: Influence of the Gall Bladder, Oddi's Muscle and the Duodenum upon the Outflow of Bile, Jap. J. Gastroenterol. **5**:19, 1933.

52. Rost, F.: Die funktionelle Bedeutung der Gallenblase: Experimentelle und anatomische Untersuchungen nach Cholecystektomie, Mitt. a. d. Grenzgeb. d. Med. u. Chir. **26**:710, 1913. Westphal, K.: Muskelfunktion, Nervensystem, und Pathologie der Gallenenwege, Ztschr. f. klin. Med. **96**:22, 1923. Footnote 51.

53. Ivy, A. C., and Sandblom, P.: Biliary Dyskinesia, Ann. Int. Med. **8**:115, 1934.

54. Manu-Muscel, I., and Pavel, I.: Le spasme du sphincter d'Oddi cause de certains icteres prolonges, Presse méd. **38**:1260, 1930.

55. Best, R. R., and Hicken, N. F.: Biliary Dyssynergia: Physiological Obstruction of the Common Bile Duct, Surg., Gynec. & Obst. **61**:721, 1935.

56. Doubilet, H., and Colp, R.: Resistance of the Sphincter of Oddi in the Human, Surg., Gynec. & Obst. **64**:622, 1937.

was found. Duodenal lavage with magnesium sulfate was found to relax the sphincter, while hydrochloric acid caused temporary sphincter spasm, which can be prevented by atropinization. Morphine produces severe spasm lasting as long as four hours, with the pressure reaching 300 mm. of water during the second hour, after 16 mm. have been injected subcutaneously. The action of papaverine and epinephrine was found to be slight.

While there is disagreement as to the frequency with which bile can be held responsible for the development of acute hemorrhagic pancreatitis, all agree that if bile is injected under force into the pancreatic duct experimentally it can produce the condition, as was shown by Opie [33] and since then by many others. The experiments of Flexner [57] and those of other investigators demonstrate that the same result follows the injection of a wide variety of substances, such as oil (Oser,[21] Hess,[58] Guleke,[59] Eppinger [60] and Hewlett [61]), bile (Opie,[33] Flexner,[57] Guleke,[59] Oser [21] and Polya [62]), hydrochloric acid and intestinal secretion (Hlava,[63] Flexner and Pearce,[57] Hildebrand [64] and Rosenbach [65]), intestinal secretion and pancreatic juice, commercial trypsin, calcium and sodium chloride (Polya[62]), sulfuric acid (Flexner and Pearce[57]), nitric acid (Flexner and Pearce [57]), zinc chloride (Lattes [66]), chromic acid (Lattes [66]), solution of formaldehyde (Flexner and Pearce [57]), calcium chloride (Binet and Brocq [67]) and oleic acid (Hess [58] and Trevor [68]). The same results have been obtained by injecting into the blood vessels substances such as oil, paraffin, wax and lycopodium (Panum,[69] Lépine,[70] Bunge [71] and Guleke [59]). Sailer and Speese [72] suggested that this great variety of substances that cause pancreatic necrosis on injection into the ducts is proof that mechanical distention and injury to the pancreatic tissue are the destructive agents. However, the following substances have been injected into the ducts without harmful effects: blood (Flexner and Pearce [57]) and (Guleke [59]), blood serum (Flexner and Pearce [57]), glycerin (Hess [58]), paraffin (Hess [58]), agar (Lattes [66]) and starch (Hess [58]).

While quantities of 4 to 30 cc. of bile and other fluids were injected forcibly into the pancreatic duct with a syringe, Rich and Duff [2] have shown that injections of smaller quantities of India ink into the pancreatic duct will rupture the smaller ducts and acini even in a large dog, leading to the immediate escape of ink into the interstitial tissues throughout the greater part of the pancreas. Archibald [73] was unable to produce necrosis or hemorrhagic pancreatitis by injecting small amounts (0.75 cc.) of bile into the pancreatic duct. Nordmann,[74] realizing the

57. Flexner, S.: The Constituent of the Bile Causing Pancreatitis and the Effect of the Colloids upon Its Action, J. Exper. Med. **8**:167, 1906; Experimental Pancreatitis, Bull. Johns Hopkins Hosp. **9**:743, 1900; On the Occurrence of the Fat-Splitting Ferment in Peritoneal Fat Necroses and the Histology of These Lesions, J. Exper. Med. **2**:413, 1897. Flexner, S., and Pearce, R. M.: Experimental Pancreatitis, Univ. Pennsylvania M. Bull. **14**:193, 1901.

58. Hess, O.: Experimenteller Beitrag zur Aetiologie der Pankreas- und Fettgewebsnekrose, München. med. Wchnschr. **50**:1905, 1903; Experimentelles zur Pankreas und Fettgewebs-Nekrose, ibid. **52**:544, 1905.

59. Guleke, N.: Demonstration einer experimentell gewonnenen Pankreasnekrose, Berl. klin. Wchnschr. **41**:682, 1905; Ueber die experimentelle Pankreasnekrose und die Todesursache bei acuten Pankreaserkrangungen, Arch. f. klin. Chir. **75**:845, 1905-1906; **85**:615, 1908.

60. Eppinger, H.: Zur Pathogenese der Pankreasfettgewebsnekrose, Ztschr. f. exper. Path. u. Therap. **2**:216, 1905-1906.

61. Hewlett, A. W.: On the Occurrence of Lipase in the Urine as a Result of Experimental Pancreas Disease, J. M. Research **11**:1904.

62. Polya, E. H.: Zur Pathogenese der acuten Pancreasblutung und Pankreasnekrose, Berl. klin. Wchnschr. **43**:1562, 1906; Ueber die Pathogenese der akuten Pankreaserkrankungen, Mitt. a. d. Grenzgeb. d. Med. u. Chir. **24**:1, 1912.

63. Hlava, J.: Some Affections of the Pancreas and Sudden Death from Them, Sbírka přednášek. z oboru lékarsk., v Praze, 1899, no. 16, p. 111; Sur la pancréatite hémorrhagique, Compt. rend. Cong. internat. de méd. (1897) (sect. 3) **2**:106, 1899.

64. Hildebrand, G.: Zur Pankreaschirugie, Arch. f. klin. Chir. **89**: 2, 1909.

65. Rosenbach, F.: Gallenstauung im Ductus Wirsungianus durch Stein in der Papilla Vateri als Ursache einer akuten Pankreasnekrose mit galliger Peritonitis, München. med. Wchnschr. **65**:185, 1918.

66. Lattes, L.: Ueber Pankreasvergiftung, Virchows Arch. f. path. Anat. **211**:1, 1913.

67. Binet, L., and Brocq, P.: Le rôle du suc intestinal dans la réproduction expérimentale de la pancréatitie hémorragique avec stéatonecrose, Compt. rend. Soc. de biol. **83**:340, 1920.

68. Trevor, R. S.: Some Recent Work on Disease of the Pancreas, Practitioner **72**:570, 1904.

69. Panum, P. L.: Experimentelle Beiträge zur Lehre von der Embolie, Virchows Arch. f. path. Anat. **25**:308, 1862.

70. Lépine, R.: Diabète maigre avec intégrité du pancréas, Lyon méd. **71**:591, 1892.

71. Bunge: Zur Pathogenese und Therapie der acuten Pankreashämorrhagie und abdominalen Fettgewebsnekrose, Arch. f. klin. Chir. **71**:726, 1903.

72. Sailer, J., and Speese, J.: Acute Pancreatitis, Tr. A. Am. Physicians **23**:540, 1908.

73. Archibald, E. W., in Lewis, D.: Practice of Surgery, Hagerstown, Md., W. F. Prior Company, Inc., 1933, vol. 7, p. 1.

74. Nordmann, O.: Experimente und klinische Betrachtungen über die Zusammengänge zwischen acuter Pankreatitis und Erkrankungen der Gallenblase, Arch. f. klin. Chir. **102**:66, 1913.

danger of the injection technic, converted the common duct and pancreatic duct into a continuous channel by closing the ampulla of Vater with a purse string suture. Jaundice without hemorrhagic pancreatitis occurred, even though the pancreatic duct was dilated with bile. Mann and Giordano [41] likewise found that if 5 to 10 cc. of bile is forced with a syringe into the pancreatic duct of a dog rupture of the smaller ducts and acini occurs.

Even if the ampulla is obstructed and the ducts converted into a communicating system, will bile flow into the pancreatic duct? Theoretically, it would seem that the direction of flow should depend on the relative pressures developed in the duct system of each gland. Mann and Giordano [41] were unable to inject bile into the pancreatic duct of a dog with the maximal normal secretory pressure of the liver, 350 mm. of bile. The secretory pressure in the pancreatic duct was found to range from 260 to 350 mm. of water. These values are in accord with those of other investigators.[75] It is seen that the maximal secretory pressures of the liver and pancreas are about equal, the former being slightly higher, the difference, however, being possibly great enough to cause bile to flow over into the pancreatic duct. When pressures up to 800 mm. of bile were used, even though the pancreatic duct was filled with bile, acute pancreatitis did not result. Considerable importance has been attached to the observation of Mann and Giordano [41] that during vomiting the pressure in the biliary tract rose to 1,000 mm. of bile, and the suggestion has been made that through such a mechanism vomiting might be thought to cause pancreatic necrosis. It is, however, altogether probable that the general increase in intra-abdominal pressure due to vomiting would affect the two glands alike and no transfer of fluid would occur. Harms [76] reported that during the height of digestion in the unanesthetized dog the secretory pressure of the pancreas is higher than that of the liver, a finding which would suggest the passage of pancreatic juice into the biliary channels, rather than the reverse.

From these experiments, the conclusion that hepatitis or cirrhosis of the liver is due to a passage of pancreatic juice into the bile duct would seem almost as justifiable as that pancreatitis is due to a reflux of bile.[77] Bile may pass into the pancreatic duct for one or all of the following reasons: The secretion of bile is continuous, with changes in rate, while the secretion of the pancreatic juice is intermittent. There are times when the pressure in the pancreatic duct might be considerably less than in the bile duct. The liver has firmer tissue and a stronger capsule than the pancreas. With regard to the volume of fluid secreted, the drainage of the intraductal fluid to the outside of the gland is freer in the pancreas than in the liver. From our study of the pancreatic systems, we found that in 11 per cent the main and accessory ducts did not communicate and in 23 per cent the minor papilla was closed, making a total of 34 per cent in which fluid could not pass from the main duct to the duodenum by way of the accessory duct. These findings are in accord with those of other investigators.[78]

Current theories postulate that bile entering the pancreatic duct in man produces necrosis of the pancreas because of its own irritating and necrotizing properties or its bacterial content or because it activates the inactive trypsinogen of the normal pancreatic secretion while the latter is still in the pancreatic ducts. Persons who emphasize the role of infection introduced by the reflex of bile contend that necrosis of the pancreas is produced either through the direct action of the bacteria or through the destructive effects of trypsin, which follow on the activation of trypsinogen by the bacteria or their products. All authors agree that the peculiar characteristics of the fat necrosis which accompany hemorrhagic pancreatitis depend on the action of pancreatic lipase which is secreted in active form and which escapes into the tissues when necrosis of the pancreas occurs.

The various theories regarding the hemorrhage of acute hemorrhagic pancreatitis are discussed by Gruber.[79] Some authors believe that

75. Herring, P. T., and Simpson, S.: The Pressure of Bile Secretion and the Mechanism of Bile Absorption in Obstruction of the Bile Duct, Proc. Roy. Soc., London **79**:517, 1907; The Pressure of Pancreatic Secretion, and the Mode of Absorption of Pancreatic Juice After Obstruction of the Main Ducts of the Pancreas, Quart. J. Exper. Physiol. **2**:99, 1909. Mann, F. C., and Foster, J. P.: The Secretory Pressure of the Liver, with Special Reference to the Presence or Absence of a Gallbladder, Am. J. Physiol. **47**:278, 1918. Mitchell, W. T., Jr., and Stifel, R. E.: The Pressure of Bile Secretion During Chronic Obstruction of the Common Duct, Bull. Johns Hopkins Hosp. **27**:78, 1916.

76. Harms, E.: Ueber Druckmessungen im Gallen- und Pankreasgangsystem, Arch. f. klin. Chir. **147**:637, 1927.

77. Diseases of the Liver, Pancreas, and Suprarenal Glands, in Nothnagel, C. W. H.: Encyclopedia of Practical Medicine, Philadelphia, W. B. Saunders Company, 1903, p. 642.

78. Schirmer [5] Veslingius and others.[9] Baldwin.[26]

79. Gruber, G. B., in Henke, F., and Lubarsch, O.: Handbuch der speciellen pathologischen Anatomie und Histologie, Berlin, Julius Springer, 1929, vol. 5, pt. 2.

the hemorrhage is the result of a vasomotor reflex; others believe that it results from venous thrombosis, and still others believe that it results from the erosion of the blood vessels by the pancreatic trypsin. Rich and Duff[2] found that the specific vascular lesion causing the hemorrhage was located especially in the media of the vessel, where the muscle fibers are swollen, their nuclei pyknotic and often separated by fluid spaces. The adventitia may appear condensed and pink staining and contain polymorphonuclear leukocytes. The internal elastic membrane becomes frayed, loses its undulations and takes on a swollen appearance. The first alterations of the media are found in its outer layers, the muscle fibers of which become necrotic while those near the intima remain intact. But the process is apparently a rapid one and proceeds rapidly to involve the entire thickness of the vessel wall, with final destruction of the intima. Destruction of a segment of the vessel wall was found most frequently in the larger arteries, while destruction of the whole circumference was the rule in the smaller vessels. The lesion is quite indistinguishable from that characteristic of the familiar arteriolonecrosis and hyaline arteriolosclerosis occurring in man in association with hypertension and in arteriolosclerotic nephritis.

SUMMARY

The historical aspects concerning the anatomy of the pancreas have been reiterated. The embryology of the pancreatic systems has been reviewed. The etiologic factors of pancreatitis have been discussed.

The anomalies and their results encountered in 250 dissections of the pancreatic systems are tabulated and discussed with their clinical significance. In 73 instances, about 24 per cent, there could be found no junction of the pancreatic and bile ducts, each entering the duodenum with separate orifices. In 92 instances, 37 per cent, the ducts were contiguous, the dividing septum terminating 1 to 2 mm. from the apex of their common orifice. In this group, however, a true ampulla was not considered present. In 81 instances, 32 per cent, a true ampulla was present, varying in length from 3 to 14 mm., while in 4 instances, 2 per cent, the main pancreatic duct was reduced to a fibrous cord.

In 47 instances, 18 per cent, the length of the ampulla exceeded the average diameter of the duodenal orifice, and a complete block at the papilla would convert the two ducts into a communicating system.

The average diameter of the duodenal papilla was 3 mm., with limits of 1.5 and 4.5 mm.

Concerning the accessory pancreatic duct, in only 89 of 100 specimens studied for this purpose could any intraglandular communication between the ducts be demonstrated. In 4 instances, the embryonic duct system was present—i. e., the accessory duct carried the greater part of the secretion—while the main duct was reduced to a fibrous cord, leaving 85 specimens with a normal duct arrangement. In only 62 of these, 73 per cent, was the duct found to be patent, or there were 23 instances in which the accessory duct did not communicate with the duodenum, regardless of the duct arrangement, making a total of 34 per cent in which fluid could not pass from the main pancreatic duct to the duodenum by way of the accessory duct. The average diameter of the undistended duct at its point of peroforation of the duodenum was 1.6 mm.

The anatomic position and arrangement of the sphincter of Oddi and the conditions modifying its resistance are discussed, and the current theories postulated regarding the necrosis and hemorrhage which occur are briefly discussed.

SLUDGED BLOOD IN TRAUMATIC SHOCK

I. MICROSCOPIC OBSERVATIONS OF THE PRECIPITATION AND AGGLUTINATION OF BLOOD FLOWING THROUGH VESSELS IN CRUSHED TISSUES

MELVIN H. KNISELY, PH.D.
CHICAGO

THEODORE S. ELIOT, PH.D.
MEMPHIS, TENN.

AND

EDWARD H. BLOCH, M.D.
CHICAGO

This paper is the first of a series describing some studies of the pathologic circulatory physiology of animals and men preceding and during traumatic shock. The paper has two purposes: (1) to introduce this series of studies on traumatic shock and relate them to other work from our laboratories and (2) to describe the initiation of some microscopically visible changes in the physical consistency of the circulating blood which are caused by mechanical injuries to tissues (cutting or crushing injuries) but which we have not yet found caused by hemorrhage alone.

The studies of the changes in the blood, vessel walls and circulation preceding and during traumatic shock which this paper introduces are a part of a larger series of studies of normal and pathologic circulatory physiology. Our colleagues and we have been carrying out microscopic studies of:

1. The circulation in a number of tissues and organs of laboratory animals under the most nearly normal conditions which we have thus far been able to attain experimentally. (Knisely,[1] Bloch [2] and Knisely, Bloch and Warner.[3])

2. The mechanical consistency of the circulating blood, the vasomotor behavior and the pathologic reactions of the vessel walls of the bulbar conjunctiva of (*a*) unanesthetized normal human beings and (*b*) persons with diagnoses of a wide variety of pathologic conditions and diseases (Knisely and Bloch.[4]).

3. The circulatory physiology of normal Macaccus rhesus monkeys and of monkeys infected with Plasmodium knowlesi malaria (Kni-

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From the Departments of Anatomy and Preventive Medicine of the University of Tennessee College of Medicine and the Hull Laboratory of Anatomy of the University of Chicago.

The studies on which this paper is based were made possible through support given by the Tennessee Valley Authority through the Division of Preventive Medicine of the University of Tennessee.

1. Knisely, M. H.: Apparatus for Illuminating Living Tissues and Measuring Rate and Volume of Blood Flow, Anat. Rec. (supp.) **58**:73 (March) 1934; (*b*) Microscopic Observations on Circulatory Systems of Living Transilluminated Mammalian Spleens and Parturient Uteri, Proc. Soc. Exper. Biol. & Med. **32**: 212 (Oct.) 1934; (*c*) A Method of Illuminating Living Structures for Microscopic Study, Anat. Rec. **64**: 499 (March) 1936; (*d*) Spleen Studies: I. Microscopic Observations of the Circulatory System of Living Unstimulated Mammalian Spleens, ibid. **65**: 25 (April) 1936; (*e*) Spleen Studies: II. Microscopic Observations of the Circulatory Systems of Living Traumatized Spleens, and of Dying Spleens, ibid. **65**: 131 (May) 1936; (*f*) Microscopic Observations of the Circulatory Conditions in Living Frog Liver Lobules, ibid. (supp.) **73**:69 (March) 1939; (*g*) The Histophysiology of Peripheral Vascular Beds, in Blood, Heart and Circulation, American Association for the Advancement of Science, Washington, D. C., 1940.

2. Bloch, E. H.: Some Actions of Adrenalin Chloride and Acetyl-Beta-Methyl-Choline Chloride on Finer Vessels of Living Frog Liver Lobules, Anat. Rec. (supp.) **76**:7 (Feb.) 1940.

3. Knisely, M. H.; Bloch, E. H., and Warner, L.: Microscopic Observations of Normal Blood, Vessel Walls, and Vascular Reactions, the Testing of Methods, and the Current Development of Operative Techniques, to be published.

4. (*a*) Knisely, M. H., and Bloch, E. H.: Microscopic Observations of Intravascular Agglutination of Red Cells and Consequent Sludging of the Blood in Human Diseases, Anat. Rec. (supp.) **82**:426 (March) 1942; (*b*) Intravascular Agglutination of Erythrocytes in Disease, with Cinema Demonstration, Proc. Inst. Med. Chicago **15**:281 (March 15) 1945.

sely, Stratman-Thomas and Eliot [5] and Knisely, Stratman-Thomas, Eliot and Bloch.[6]

4. The reactions of various parts of the vascular system during and following hemorrhage initiated with a minimum amount of mechanical trauma to animals (unpublished).

5. The reactions of the blood and vascular system and the changes in the circulation following mechanical trauma made with a minimum amount of hemorrhage from animals.

Thus, we have been studying normal blood and vessel walls, surveying the condition of these in a number of diseases and trying to study the sequence of circulatory phenomena seen in hemorrhagic shock uncomplicated by trauma, the sequence in traumatic shock uncomplicated by hemorrhage, and the pathologic circulatory phenomena in P. knowlesi malaria uncomplicated by either trauma or hemorrhage. The over-all purposes are, of course, to recognize as many factors as possible of normal and of pathologic circulatory physiology and to determine the kinds, magnitudes and sequences of pathologic factors present in each pathologic complex.

Our studies of the changes in blood and vessel walls preceding and during traumatic shock are a direct outgrowth of the microscopic studies of the pathologic circulatory physiology of rhesus monkeys during acute P. knowlesi malaria (see Knisely, Stratman-Thomas, Eliot and Bloch [6] and the motion picture "Knowlesi Malaria in Monkeys" [7]). As outlined in the following paragraphs, the studies on malaria provided background for and clues to follow in this series of studies on traumatic shock.

5. Knisely, M. H.; Stratman-Thomas, W. K., and Eliot, T. S.: Observations on Circulating Blood in the Small Vessels of Internal Organs in Living Macaccus Rhesus Infected with Malarial Parasites, Anat. Rec. (supp.) **79**:90 (March) 1941.

6. Knisely, M. H.; Stratman-Thomas, W. K.; Eliot, T. S., and Bloch, E. H.: Knowlesi Malaria in Monkeys: I. Microscopic Pathological Circulatory Physiology of Rhesus Monkeys During Acute Plasmodium Knowlesi Malaria. J. Nat. Malaria Soc. **4**: (Dec.) 1945.

7. At several points in this paper there are references to scenes in the motion picture "Knowlesi Malaria in Monkeys." This 16 mm. Kodachrome motion picture, taken through the microscope, records several scenes of normal unagglutinated blood and normal vessel walls and then traces one set of factors of pathologic circulatory physiology through lethal stages. The picture was made to make it possible to demonstrate some of our findings to physicians and medical scientists. It usually takes about sixty minutes to project the film. Copies of this film will be loaned free, except for transportation charges, to medical schools, medical societies, medical officers of the military services and research groups. Requests should be sent either to Dr. M. H. Knisely, Department of Anatomy, University of Chicago, or to Dr. T. S. Eliot, Department of Anatomy, University of Tennessee, Memphis, Tenn.

METHODS

Two methods are being used for studying the blood and small vessels with microscopes. One is the fused quartz rod method of illuminating living tissues for microscopic study (Knisely [8] and Hoerr [9]), which permits routine study in many internal organs of experimental animals at 32, 48, 96, 240 and 400 and less frequently at 600 diameters' magnification. The other consists in focusing stereoscopic dissection microscopes (32, 48 and 96 diameters) on the obliquely illuminated nictitating membrane and/or bulbar conjunctiva of anesthetized animals or unanesthetized human beings. A Zeiss scale in one ocular permits rapid or continuous close estimates of the dimensions of structures observed.

At all times the blood coming down the arterioles of uninjured bulbar conjunctiva is a statistically valid sample of all the flowing arterial blood in the body. This was determined by opening an animal and studying the blood passing through many different organs. In frogs, observations under various approximately physiologic and known experimentally produced pathologic conditions have been made of the vessels and blood in skin, brain, peripheral nerves, smooth muscle of the gastrointestinal tract, gastric mucosa, mesenteries, striated muscles, lung, adrenal gland tissue, kidney and liver (for operative technics see Knisely, Bloch and Warner [3]). In mammals, observations have been carried out in the surface of brain, omentum, mesenteries, striated muscles, smooth muscles of the gastrointestinal tract, intestinal mucosa, uterus, ovary, spleen and liver. These studies have been carried out over a fourteen year period. At any one time, the blood coming down the arterioles of all organs of an animal has the same mechanical consistency. In about 3,500 frogs, in 1,100 salamanders (Amblystoma), in 500 small laboratory mammals—mice, rats, guinea pigs and cats (Knisely [1e])—and in 50 rhesus monkeys (Knisely, Stratman-Thomas, Eliot and Bloch [6]), this has always been true. Hence, the blood coming

8. (*a*) Knisely; [1e] (*b*) The Fused Quartz Rod Method of Illuminating Living Structures for Microscopic Study, in McClung, C. E.: Handbook of Microscopical Techniques for Workers in Animal and Plant Tissues, ed. 2, New York, Paul B. Hoeber, Inc., 1937, pp. 632-642; (*c*) An Improved Fused Quartz Rod Living Tissue Illuminator, Anat. Rec. **71**:503 (Aug.) 1938.

9. Hoerr, N. L.: Illumination of Living Organs for Microscopic Study, in Glasser, O.: Medical Physics, Chicago, The Year Book Publishers, Inc., 1944, p. 625.

down the arterioles of any organ, such as the uninjured bulbar conjunctiva of human beings, may be studied as a valid sample of all the flowing arterial blood in the body. This is a key fact, for it permits rather close integration of some phases of laboratory and clinical studies of normal and pathologic circulatory physiology.

By the coordinated use of these two methods, changes in the mechanical consistency of the circulating blood and the reactions of the walls of small vessels can be traced (E. R. and E. L. Clark[10]) with anesthetics and operations in animals and with or without anesthetics or operations in men, during phases of normal physiologic processes, during untreated pathologic processes and diseases, and during and following the administration of standard or of experimental therapeutic agents and/or procedures.

CONTROLS AND BACKGROUND

For a brief but clear introduction to the changes in the blood and vessel walls following mechanical trauma, which if sufficiently severe, progressive, prolonged and untreated leads to "traumatic shock," three sets of concepts are necessary: (*a*) concepts of normal blood and vessel walls, because clearcut concepts of the normal are necessary as a foundation for recognizing transitions into the pathologic; (*b*) concepts of the normal ranges of the diameters of terminal arterioles, capillaries and arteriovenous anastomoses, and (*c*) concepts of the changes in the blood and the vessel walls of rhesus monkeys during stage III of acute P. knowlesi malaria. Some features of the pathologic processes of traumatic shock closely parallel certain features of stage III of this malaria.

A. Concepts of Normal Blood and Vessel Walls.—In the internal organs of about 3,500 frogs, 1,100 salamanders (Amblystoma), 500 normal small laboratory mammals anesthetized with sodium amytal (Knisely[15]) and several normal rhesus monkeys anesthetized with pentobarbital sodium (Knisely, Stratman-Thomas, Eliot and Bloch[6]) and in the bulbar conjunctiva of 50 normal unanesthetized medical students and student nurses (Knisely and Bloch[4b]):

1. The circulating red cells were not agglutinated. Each was free from the others. They tended to repel each other slightly (Arey[11] and Abramson, Moyer and Gorin,[12] pp. 307-319).

2. No white cells stuck to the inner surfaces of the walls of small vessels. The inner surfaces of the linings of normal small vessels were smooth and clean. This agrees with and extends to other organs and species in the observations of E. R. and E. L. Clark.[10]

3. The flow of the unagglutinated blood was laminar, or "streamlined" (see Poiseuille,[13] figure 6, and Knisely, Bloch and Warner[3]).

4. The small normal vessels did not leak appreciable amounts of fluid for (*a*) there was no visible hemoconcentration occurring (see Krogh,[14] p. 14); (*b*) in the mesenteries and omentum of animals, the fat cells outside vessels were tight together; they were not being pushed and held apart by escaping fluid, and (*c*) in human beings the bulbar conjunctiva was not forced up and held away from the sclera, whereas this does occur and can easily be seen with stereoscopic microscopes in human beings at times when the bulbar conjunctival vessels are seen to be leaking rapidly.

5. The blood flowed so rapidly in most arterioles and venules which were from 60 to 120 microns in diameter that individual red cells could not be seen.

The observations of unagglutinated blood in normal human beings are particularly valuable as strict controls for animal experiments because the normal human beings had not been subjected to fright or to anesthetics or operations.

With routine care, it is possible with the fused quartz rod method to keep the exposed tissues and organs of normal rhesus monkeys anesthetized with pentobarbital sodium under continuous observation for fourteen to eighteen hours without causing any of the microscopically visible evidences of injury to the blood (see the following sections) or vessel walls (E. R. and E. L. Clark[10]). Normal unagglutinated circulating blood and normal vessel walls of monkeys have been recorded in motion pictures (see reel 1 of the Knowlesi Malaria film[7]).

B. The Diameters of the Smallest Vessels.—In most organs of a number of mammalian species, those capillaries through which blood is flowing normally vary from a little more than

10. Clark, E. R., and Clark, E. L.: Observations on Changes in Blood Vascular Endothelium in the Living Animal, Am. J. Anat. **57**: 385 (Nov.) 1935.

11. Arey, L. B.: Observations on the Shape of the Erythroplastids in the Wing of the Bat, Anat. Rec. **14**: 135 (Jan.) 1918.

12. Abramson, H. A.; Moyer, L. S., and Gorin, M. H.: Electrophoresis of Proteins and Chemistry of Cell Surfaces, New York, Reinhold Publishing Corporation, 1942.

13. Poiseuille, J. L. M.: Recherches sur les causes du mouvement du sang dans les vaisseaux capillaires, Mém. Acad. d. sc., Paris **7**:105, 1841.

14. Krogh, A.: The Anatomy and Physiology of Capillaries, ed. 2, New Haven, Conn., Yale University Press, 1929.

once to a little more than twice or even two and a half times the diameter of the red cells which pass through them. The red cells usually pass in single file or, at most, a double row. When a capillary contracts or is compressed to just a little less than the diameter of the contained red cells, the red cells rub on the inner surface of the endothelium and thus resist passage, and the flow through that vessel soon stops (see Krogh,[14] page 11, and Knisely [15]). Most true capillaries can dilate without losing tonus, weakening and sacculating to a little more, but usually not much more, than two or two and a half times the diameter of the contained red cells (Krogh,[14] p. 335, and Knisely, Stratman-Thomas, Eliot and Bloch [6]). The arterioles of most of the organs in frogs and mammals which we have studied are long, narrow, tapering cones. During the flow of blood through them, their outlet tips vary either anatomically or functionally from a little wider to a little narrower than the capillaries or sinusoids they join and supply. These statements are true of the arterioles and capillaries of the bulbar conjunctiva of human beings and almost certainly true of the arterioles and capillaries of many other human organs during life. Arteriovenous anastomoses have thus far been found in but a few organs of any one species. The arteriovenous anastomoses which have been found are often closed and when open are frequently but two or three times the diameter of the red cells passing through them (see the reviews by E. R. Clark [15] and Boyd [16]). These are key points for understanding some of the pathologic processes initiated by intravascular agglutination of the blood, for they show that most of the time, under most conditions, nearly all the circulating blood must pass through vessels having an internal diameter from about once to twice or at most three times that of the red cells on every trip from the left side of the heart through the circulatory system and return. Thus, as is well known but not always remembered, the arterioles and capillaries are a perpetual "bottleneck" in the vascular system.

C. Some Changes in the Blood and Vessel Walls During Stage III of P. knowlesi Malaria.—At the beginning of stage III of the pathologic circulatory physiology of rhesus monkeys with P. knowlesi malaria, a thick, glassy precipitate forms between and around all the blood cells of the animal. In this malaria, this precipitate forms throughout all of the animal's circulatory system at one time. The process acts as though it were autocatalytic; once it starts, it usually goes on to completion in from ten to about twenty minutes. This precipitate binds the animal's red cells together in wads and masses (*not rouleaux*), which by microscopic standards are large, semirigid and tough, and thereby rapidly changes all the animal's circulating blood into a thick, mucklike sludge.

As soon as the blood has changed to this thick, pasty sludge, a definite sequence of events takes place. Three major steps are as follows:

1. This sludge resists its own passage through small vessels much more than does normally fluid blood; consequently, the rate of flow through small vessels all over the body becomes progressively slower than the normal rates for each degree of dilatation of each vessel. This increased resistance to flow and consequent reduced rates of flow through the capillary beds slowly, progressively and inescapably leads to various degrees of stagnant anoxia all over the body.

2. There is a time interval of variable length during which (*a*) the reduced rates of flow are unmistakable and (*b*) there is still no visible hemoconcentration of the sludge passing through peripheral vascular beds. During this period, the flow through each small vessel is slower than the normal rate for whatever degree it is dilated but the vessels have not yet begun to leak perceptibly (see the scenes following titles 29, 30 and 31 in the Knowlesi Malaria film [7]). After the sludged blood has been flowing too slowly for a time, the walls of postcapillary venules and small venules lose their ability to retain blood colloids. Anoxia of the endothelium is alone sufficient to cause this (see Starr [17]; Starling [18]; Landis [19]; Krogh,[14] pp. 321, 326 and 335; Maurer [20]; Warren and Drinker [21]; Drinker,[22]

15. Clark, E. R.: Arterio-Venous Anastomoses, Physiol. Rev. **18**: 229 (April) 1938.

16. Boyd, J. D.: Arterio-Venous Anastomoses, London Hosp. Gaz. (Clin. Supp.) **42**:i (July) 1939.

17. Starr, I., Jr.: Production of Albuminuria by Renal Vasoconstriction in Animals and Man, J. Exper. Med. **43**: 31 (Jan.) 1926.

18. Starling, E. H.: Principles of Human Physiology, ed. 4, Philadelphia, Lea & Febiger, 1926, p. 854.

19. Landis, E. M.: Micro-Injection Studies of Capillary Permeability: III. The Effect of Lack of Oxygen on the Permeability of the Capillary Wall to Fluid and to the Plasma Proteins, Am. J. Physiol. **83**: 528 (Jan.) 1928.

20. Maurer, F. W.: The Effects of Decreased Blood Oxygen and Increased Blood Carbon Dioxide on the Flow and Composition of Cervical and Cardiac Lymph, Am. J. Physiol. **131**: 331 (Dec.) 1940; The Effects of Carbon Monoxide Anoxemia on the Flow and Composition of Cervical Lymph, ibid. **133**:170 (May) 1941; The Effects of Anoxemia Due to Carbon Monoxide

(Footnotes continued on next page)

and I. Bloch,[23] and in a variety of unpublished experiments of ours sufficiently severe anoxia always caused endothelium to leak fluids rapidly. The larger and more rigid the masses of precipitate-coated agglutinated blood cells, the more they resist passage through the long, cone-shaped arterioles and the capillaries, the slower the flow through the peripheral vascular beds and the shorter the period before the vessel walls begin to leak perceptibly.

3. Postcapillary venules and small venules begin to leak fluid, at first slowly and later more rapidly. The vessels of some tissues and organs begin to leak before those of others. Hence, local areas begin to lose fluid, and in these local areas continuous microscopically visible hemoconcentration begins (see Krogh,[14] p. 14, and the scene following title 35 in the Knowlesi Malaria film [7]). At first the fluid being lost through the walls of postcapillary venules and small venules can be returned to the blood vascular system by way of lymphatics as fast as it is lost. Later, rapid local fluid losses and local hemoconcentrations occur all over the body, and, finally, as a result of rapid local fluid losses, enormous numbers of small vessels are left plugged with stranded masses of precipitate-coated, tightly agglutinated blood cells.

As a result of these processes, the sum of the rates of local fluid losses becomes greater than the sum of the rates of return of fluids to the blood by lymphatics. Hence, at the same time that enormous numbers of small vessels are being plugged with stranded masses of coated, agglutinated red cells, there is a progressively decreasing intravascular plasma volume. The stranding of precipitate-coated masses of red cells *in* small vessels and fluid loss *from* small vessels are major factors causing a progressively decreasing circulating blood volume and venous return (see Knisely, Stratman-Thomas, Eliot and Bloch [6] and reel III of the Knowlesi Malaria film).

When fine droplets of india ink are injected into the blood stream of frogs, each small droplet immediately receives a complete coating of a clear, glassy precipitate formed from the frog's plasma. This coating is not sticky to the red cells it bumps or to ordinary undamaged vascular endothelium, but it is extremely sticky to the inner surface of the sinusoid-lining Kupffer cells of living frog liver. When and wherever this coating material touches the inner surface of the hepatic sinusoid lining, it sinks with its contained ink into the cytoplasm of the lining. The ingestion of a bit of this coating appears to be as fast as that when a small sphere of mercury touches and merges with and into a larger one (see Knisely, Bloch and Warner [24] for more details). During stage III of P. knowlesi malaria in monkeys, coatings are precipitated around normal circulating red cells, and these coatings are ingested with the contained erythrocytes by the phagocytes of the liver, bone marrow and spleen. In monkeys, the rapid ingestion of coated erythrocytes (*a*) contributes to decreased red cell counts (anemia) and (*b*) assists in progressively decreasing the circulating blood volume.

In summation, the controls and background for the subsequent observations of the effects of mechanical trauma are:

1. In normal animals and men, the blood cells are not agglutinated, the red cells repel each other slightly and the white cells do not stick to vessel walls. The walls of capillaries, postcapillary venules and venules do not leak rapidly enough to be detected by microscopic observation.

2. Most of the time, under most conditions, nearly all the circulating blood must, because of the anatomy and dimensions of the peripheral parts of the living vascular system, pass through vessels having an internal diameter from about once to twice or at most three times that of the red cells on every trip around the circulatory system.

3. In monkeys with P. knowlesi malaria, at the beginning of stage III, (1) a precipitate is formed between and around all the blood cells, coats them and binds them together in great semirigid wads and thereby changes all the circulating blood to a thick, mucklike sludge. The formation of this particular malaria sludge usually takes but ten to twenty minutes. (2) The heavily sludged blood flows more and more

and Low Oxygen on Cerebrospinal Fluid Pressure, ibid. **133**:180 (May) 1941.

21. Warren, M. F., and Drinker, C. K.: The Flow of Lymph from the Lungs of the Dog, Am. J. Physiol. **136**:207 (March) 1942.

22. Drinker, C. K.: The Lymphatic System, Stanford University, Calif., Stanford University Press, 1942, pp. 78-84.

23. Bloch, I.: Some Preliminary Considerations Concerning Concentration of Oxygen in Tissue, Bull. Mathemat. Biophysics **3**: 121 (Dec.) 1941; Some Theoretical Considerations Concerning the Interchange of Metabolites Between Capillaries and Tissue, ibid. **5**: 1 (March) 1943.

24. Knisely, M. H.; Bloch, E. H., and Warner, L.: Selective Phagocytosis: I. Microscopic Observations of the Selective Phagocytic Removal of Coated Particles from Flowing Blood by the Sinusoid Lining Cells of Living Frog Liver, to be published.

slowly, but for a time the walls of vessels do not leak perceptibly. (3) When the flow has been slow enough for a long enough time, postcapillary venules begin to leak, at first slowly and then more rapidly. (4) Venule walls leak so rapidly that masses of coated cells are left stranded in the vessels. (5) The stranding of coated masses in vessels and loss of fluid from vessels causes a progressively decreasing circulating blood volume and venous return. (6) The rapid ingestion of coatings containing erythrocytes by the phagocytes of liver, bone marrow and spleen acts toward causing and maintaining (*a*) low red cell counts (anemia) and (*b*) progressively decreasing circulating blood volume.

How Studies of Malaria Led to Studies of Traumatic Shock.—When the formation of the stage III precipitate was seen with the microscope in a living monkey infected with P. knowlesi, the chemical and immunologic natures of the precipitate immediately became important problems. Consequently, samples of this heavily sludged stage III blood were drawn into oiled and heparinized or oiled and citrated syringes, injected into little petrolatum-ringed pools of citrated mammalian Ringer solution on microscope slides and examined by direct light and by dark field illumination.

In the living animal, all the red cells were held together in wads and masses. On the slide, not more than two minutes afterward, some clumps had separated; the rapid, forcible swirling of the blood as it passed into and out of the syringes and/or the solutions used caused many clumps to disintegrate into individual red cells. However, many masses of clumped red cells remained. By transillumination in vitro, the material which held these clumps together was not visible. By dark field illumination, it was obvious that a thick, glassy, cottony precipitate was present between and around all the red cells of each clump. (This is shown in the Knowlesi Malaria film following title 48 *a*).

Bloch pulled some of these clumps apart with a Chambers microdissector (see Chambers and Kopac,[25] pp. 62-109). The precipitate which held the erythrocytes together was fairly abundant and had a stringy or gluey or tarry consistency. By microscopic standards, it was rather tough. The appearance and consistency of the precipitate suggested that it might be largely fibrin or some fibrin-like material. Consequently, we decided to try to form some fibrin within the vascular system of a normal monkey to see what freshly formed, intravascular fibrin would look like in the living animal.

25. Chambers, R., and Kopac, M. J.: Micrurgical Technique for Study of Cellular Phenomena, in McClung, C. E.: Handbook of Microscopical Techniques for Workers in Animal and Plant Tissues, ed. 2, New York, Paul B. Hoeber, Inc., 1937, pp. 62-109.

MICROSCOPIC EXPERIMENTS WITH MECHANICAL TRAUMA

1. Experimental Crushing of Monkey Omentum.—A young, vigorous male monkey was selected and anesthetized with pentobarbital sodium given intrapleurally.[26]

When the animal was asleep, an eyelid was reflected (its tarsal plate keeps it flat) and the reflected portion transilluminated with a fused quartz rod to permit microscopic study of the circulating blood and the vessel walls of the inner surface of the eyelid. This area was than studied at 32, 48 and 96 diameters to see whether the blood and the vessel walls were normal. During these observations, made to help select a normal experimental animal and as controls for possible effects of the laparotomy which followed, the vessel walls and the blood flowing in them looked perfectly normal, for (*a*) the circulating red blood cells were not agglutinated, (*b*) each red cell which bumped a vessel bifurcation turned over easily, demonstrating that the plasma viscosity was within the normal range, (*c*) no white cells were sticking to the walls of small vessels, (*d*) no visible hemoconcentration was occurring in any small vessel, (*e*) there were no emboli in this area and no minute thromboses and (*f*) the flow of the normal unagglutinated blood in small venules was laminar, or "stream-

26. We did not want an anesthetic solution in high concentration on omental tissues which were to be observed with microscopes, and the rates of absorption from subcutaneous fascias are irregular and unpredictable. Solutions of crystalloids are absorbed rapidly from the pleural space, probably because (*a*) the outer surface of the lung has great numbers of capillaries, (*b*) the lateral pressure within lung capillaries is much less than that of the inwardly directed oncotic "attraction" force of the dissolved blood proteins, (*c*) the flow through these vessels is rapid and (*d*) there is a continuous mixing and spreading of films of fluid in the pleural space due to the respiratory excursions of the lung. Hence, the pentobarbital sodium was given intrapleurally.

The calculated dose of pentobarbital sodium is divided into fourths. At first, two quarter-doses are given; after fifteen minutes, the third quarter, and after fifteen minutes more, the fourth quarter-dose. A fifth quarter-dose is given later if necessary and an additional quarter-dose or eighth-dose given whenever necessary. This maintains a controlled, nearly even anesthesia. Care must be taken (*a*) to avoid the intercostal arteries and veins to prevent hemorrhage (a small needle [no. 27] is less apt to injure an artery than a large one), (*b*) to be sure to go all the way through the intercostal muscles and reach the intrapleural space and (*c*) to be sure not to injure the lung. As the lung has a wide respiratory excursion, it can be snagged on an inwardly projecting needle; the needle should not be pushed in any farther than necessary. We ground needle tips off a little to a smooth, rounded point, which can be pushed through the skin and muscle but is more apt to indent than to cut the resilient lung tissue.

lined." Thus, these observations did not detect any abnormality of the circulating blood or vessel walls.[27]

The monkey was then opened, with minimal blood loss, by a median abdominal incision, and a fold of omentum was gently drawn out and a portion spread over a horizontal loop of stiff, paraffin-coated copper wire. The loop supported an area of omentum 1½ inches (3.8 cm.) in diameter and held this area a short distance from the abdomen. The intervening omentum was left slack so that the animal's respiratory movements were not transmitted to the supported omentum.

The exposed omentum was protected with flowing (Knisely [8b]) mammalian Ringer solution at body temperature and the tip of a quartz rod illuminator brought up under the supported area so that portions of it could be studied with microscopes. The whole supported area was then studied microscope field by microscope field at 32, 48 and 96 diameters. During these control observations, the blood and vessel walls were normal, according to each of the criteria previously listed. Thus, no single factor or combination of factors of the anesthetic, the laparotomy, the withdrawing of the omentum and the transillumination of the area were sufficiently injurious to cause any of the known microscopically visible reactions of blood or vessels to injury (E. R. and E. L. Clark [10] and Knisely, Bloch and Warner [3]).

There were a few small injured vessels at the periphery of the supported area where the omentum had been bumped against the paraffined wire. These showed the pathologic stasis described by Florey [28] and Krogh,[14] p. 14.

In the omentum of Macaccus rhesus monkeys, each small artery is accompanied by its own small vein. Pairs of these run close together for long distances. Large, powerful arteriovenous anastomoses interconnect the members of these pairs. There are so many of these arteriovenous anastomoses that, except for the capillary beds of small lymph nodes, each of which has its own blood supply, all the capillary networks of the omental tissue can be short-circuited at once. Sometimes all the arteriovenous anastomoses open and the capillaries constrict tightly shut throughout their lengths, ejecting their contents, and then contain no blood (see Krogh,[14] pages 47 to 69) and there is a rapid flow through the dilated arterioles, arteriovenous anastomoses and venules of the whole omentum. The omental vessels of this animal went into this reaction and maintained it for the rest of the period of this experiment.

An area about 3 mm. in diameter was selected at a point where an arteriovenous anastomosis joined the side of a small vein (see the figure). The tip of the quartz rod, which was about 2.5 mm. in diameter, was brought from beneath up into contact with this area, the dissection microscope was focused on the tissue and the area was then crushed by pushing and rubbing it gently against the end of the rod with the tip of a forefinger. The quartz rod is supported on springs (see Hoerr [9] for diagram); hence, it is not possible to exert much force on the tissue by pushing the omentum against the rod. The tissue was pushed against it gently and rubbed back and forth a millimeter or two, two or three times.

There were ten significant results, as follows:

1. As the finger was removed, it was found that the blood flowing through the dilated arteriovenous anastomosis (see fig.) was changing from its normally fluid state to a rather stiff sludge. Fluid blood continually came in the arterial end of the vessel, and as it passed along a somewhat viscid glassy precipitate formed between and around the red cells of the moving column. This precipitate filled the space between the red cells and, like the mortar between bricks, simultaneously held them apart and held them tightly together. Thus, the fluid blood was continually precipitated into masses of pasty sludge as it passed through this vessel of the gently crushed omental tissue. These masses were not rouleaux, although short rouleaux were often contained in them. The masses were groups of red cells bound together at all angles to each other by a nearly transparent, faintly straw-colored material. By microscopic standards, this material was very viscid and coherent. For at least an hour, all the blood passing through this vessel changed to a sludge as thick as freshly formed stage III P. knowlesi malaria sludge. The arteriovenous anastomosis was dilated to a little less than twice the diameter of the monkey's red cells; the pressure in it was high and the flow through it very rapid. Thus, for at least an hour one small vessel of the injured area was pouring a continuous rapid small stream of thickly sludged blood into the general circulation.

2. One small venule (*Th* in the figure) was thrombosed. It was solidly plugged with a mass of precipitate and red cells formed while the area was being crushed. This vessel had no flow through it; consequently it was not pouring sludge into the vascular system.

3. Other small vessels but a few tenths of a millimeter from the crushed area contained normal blood flowing normally.

4. No vessel wall ruptured; there was no diapedesis of red cells or hemorrhage into this particular injured area.

5. There was no visible hemoconcentration of the red cells passing along any of the vessels of this area; these local vessels were not leaking

27. This method of preselecting normal animals by microscopic observations before beginning experiments was instituted because we had found precipitated-agglunated, circulating red and white blood cells in a supposedly normal monkey. At autopsy that animal was found to have pulmonary tuberculosis. Human beings with pulmonary tuberculosis have one form of sludged blood. An animal with microscopically visible pathologic conditions of its vessel walls or precipitated-agglutinated circulating blood cannot be considered a normal experimental animal (Clark and Clark,[10] Knisely and Bloch;[4] Knisely, Bloch and Warner [3]).

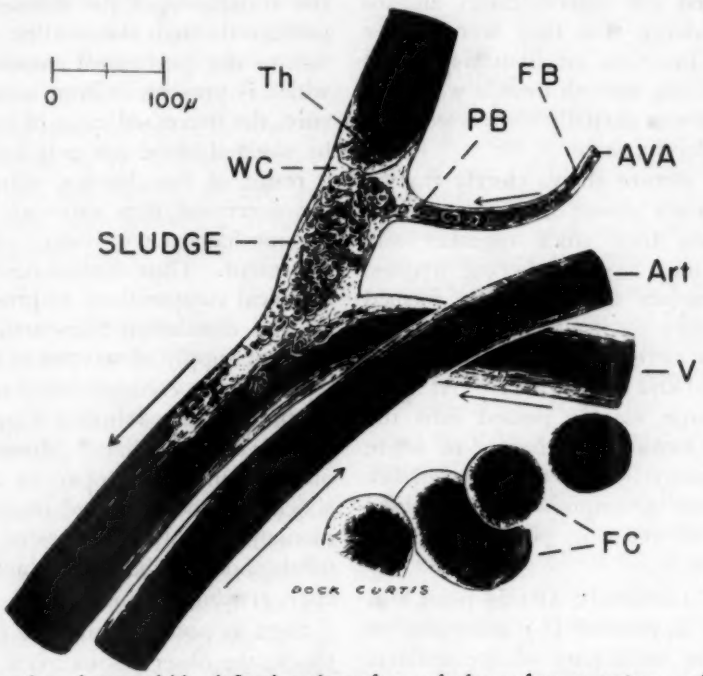
28. Florey, H.: Observations on the Resolution of Stasis in the Finer Blood Vessels, Proc. Roy. Soc., London, s.B **100**:269 (Sept.) 1926.

significantly, probably because all the vessels of the area were by microscopic standards fairly large; arterioles, arteriovenous anastomoses and venules of this size have substantial smooth muscle coats.

6. At the moment the finger was removed from the tissue, few if any white cells were sticking to the walls of injured vessels. However, many of those brought in by the flowing blood adhered to the injured walls. Hence, in a few moments white cells had accumulated one or two and even three layers deep and in irregular masses on injured endothelial surfaces (see the figure and consult E. R. and E. L. Clark [10]).

to determine the precipitation rate (Nygaard [29]), and (*c*) to record the scene for further study. The scene is somewhat underexposed, satisfactory for research purposes or private showing but not for general distribution.

Copies of this film were later spliced into loops for continuous projection to permit several persons to study the scene together, repeatedly, detail by detail. The outline of the figure is a ciné tracing of the scene, made by projecting the film onto a large sheet of drawing paper while an artist traced the outlines of the stationary structures (Brown and Sheard [30]). Thus these outlines and the scale have about the same accuracy as a good camera lucida drawing. The



Ciné-tracing of a motion picture of blood flowing through crushed monkey omentum. *Art*, artery; *V*, vein; *AVA*, arteriovenous anastomosis; *FC*, fat cells; *Th*, thrombosed venule; *WC*, masses of white cells stuck on inner surface of injured venule; *FB*, fluid blood; *PB*, precipitated blood, and *SLUDGE*, masses of precipitated-agglutinated blood. Note the scale in upper left. Arrows show direction of blood flow. The details of the precipitated-agglutinated blood were added by the artist while studying a looped continuous projection of the scene.

The adhering masses of white cells were continually being bumped by wads of the rapidly moving sludge; from time to time masses of these white cells were forced loose from the vessel lining and carried downstream to the general circulation.

This microscope field was then photographed on Kodachrome motion picture film at 24 frames per second and a Zeiss microscope scale photographed with the same lens combination, in order (*a*) to measure the dimensions of the structures present, (*b*) to find out how long it was taking fluid blood to change to thick pasty blood, i. e., following additional results were obtained from studies of the film.

7. The blood was fluid at point *FB* and rather solidly precipitated at *PB*. The precipitation end point is not exact, however, nor exactly determinable from the scene. Nor was the precipitation rate constant. Sometimes fairly solid precipitates were formed in blood which had

29. Nygaard, K. K.: Hemorrhagic Diseases—Photo-Electric Study of Blood Coagulability, St. Louis, C. V. Mosby Company, 1941.

30. Brown, G. E., and Sheard, C.: Measurements of the Skin Capillaries in Cases of Polycythemia Vera and the Role of These Capillaries in the Production of Erythrosis, J. Clin. Investigation **2**: 423 (June) 1926.

passed but halfway from *FB* to *PB*. No blood passed *PB* in the fluid state. Thus all the blood changed from a fluid to a precipitated sludge as it moved approximately 100 to 150 microns.

8. By counting the motion picture frames during which a group of blood cells passed from *FB* half or all the way to *PB*, it was found that the precipitation occurred in from one eighth to one fourth of a second. This shows how fast such precipitates can form in a living animal (consult Nygaard [29]); it does not, of course, mean that all such precipitates are formed so rapidly.

9. As the precipitated masses formed, some of them rounded up between points *FB* and *PB* and forcibly bulged the arteriovenous anastomosis; this is evidence that they were rather rigid, for an arteriovenous anastomosis of this size has a fairly strong smooth muscle wall, and at this time this one was partially contracted, i. e., in a tonic, not a flaccid, state.

10. The motion picture shows clearly that as the precipitated masses passed out of the arteriovenous anastomoses they stuck together and rapidly piled up into larger cohering masses. Thus the outer surface of the freshly formed precipitate was sticky to itself. Fragments of these large masses were intermittently torn off by the flowing blood and carried away. At short intervals whole large masses passed into the efferent venule. Occasionally masses of white cells were carried away. From the outlet orifice of the arteriovenous anastomosis, the sludged blood continually spewed out, piled up, agglutinated and passed on.

Interpretations.—Obviously, at this point this experiment can be appraised (1) according to its original purpose as a part of the malaria studies, an attempt to see what freshly formed fibrin might look like in the circulating blood, and (2) as an introduction to studies of the reactions of blood flowing through or beside injured tissues.

Looking at this experiment as a part of the malaria studies, one can conclude that a material which could be fibrin or related to fibrin looks and behaves much like the stage III P. knowlesi malaria precipitate, and in consequence all malaria precipitates should be examined both chemically and immunologically (some fibrinogens exhibit group and/or species specificities [Hektoen and Welker,[31] Kyes and Porter [32] and Kenton [33]) to determine their relationships to the fibrins.

About the time these observations were made, Dr. Harrison Rigdon pointed out in a seminar on malaria that monkeys dying of P. knowlesi malaria sometimes presented conditions at autopsy similar to Prof. Virgil Moon's [34] descriptions of the observations at autopsy in cases of traumatic shock (see Moon's 1942 summary and compare the findings he presented in his chapters IX and XI). Sludged blood occurs in a variety of pathologic conditions and diseases of human beings (see Knisely and Bloch [4]). Whenever the blood is sludged, the decreases in the rates of flow through small vessels, caused by the resistance of the masses of the sludge to passage through the smallest vessels, are a function of the mechanical consistency of the sludge which is present. Given a normal arterial pressure, the decreased rates of capillary flow caused by sludged blood are only indirectly and in part a result of the chemical sources of the sludge; the decreased flow rates are a direct result of the mechanical consistency of the sludge which is present. Thus sludges need not have identical chemical compositions to produce similar effects on (*a*) circulation rates and, consequently, (*b*) rates of supply of oxygen to endothelium.

Hence, the concepts about mechanisms causing death in monkeys during stage III of P. knowlesi malaria just outlined, Moon's accounts of the observations at autopsy in cases of traumatic shock and the described observations in crushed monkey omentum suggested a working hypothesis about mechanisms which might cause death after crushing injuries.

Seen as possible initiating factors in traumatic shock, the observations made in that microscope field in monkey omentum may be summarized as follows:

In this one tissue:

1. Crushing plus flow through a vessel in the crushed area yields a stream of sludge into the general circulation.

2. Crushing plus thrombosis of a crushed vessel yields no sludge to the venous system.

3. Flow without crush yields no sludge.

Thus, after trauma, (*a*) local crush and (*b*) flow through a vessel in the crushed area are both necessary and together are sufficient to yield a flow of sludged blood into the general circulation.

31. Hektoen, L., and Welker, W. H.: The Precipitin Reaction of Fibrinogen, J. Infect. Dis. **40**: 706 (June) 1927.

32. Kyes, P., and Porter, R. T.: The Antigenic Properties of Fibrinogens, J. Immunol. **20**:85 (Feb.) 1931.

33. Kenton, H. B.: Species Specificity of Fibrinogens, J. Immunol. **25**: 461 (Dec.) 1933.

34. Moon, V. H.: Shock: Its Dynamics, Occurrence, and Management, Philadelphia, Lea & Febiger, 1942.

4. For a time after the crush, the rate at which sludge is poured into the venous system can be as fast as the rate of flow through an open vessel in the crushed area.

5. This sludge can be formed in an area from which or into which there is (*a*) no hemorrhage and (*b*) but little loss of plasma through injured vessel walls.

6. When first formed, some of the masses have sufficient internal rigidity to bulge the walls of the vessel through which they are being forced; if not changed, such masses would resist passage through capillaries.

7. When first formed, the outer surfaces of the precipitated material are sticky to each other; hence, if not changed, masses coated with this material must, whenever they touch each other, tend to stick together and form larger masses.

8. The precipitated material contains erythrocytes and may be ingestible by the phagocytes of spleen, bone marrow and liver. If the material is phagocytosed, the contained erythrocytes would be removed from the circulatory system and destroyed.

Working Hypothesis.—Putting these bits together, one can formulate a working hypothesis about mechanisms which might cause death after crushing injuries. This hypothesis can perhaps best be stated as a set of general questions, as follows:

1. Can the crushing of tissues cause the release of substances from the crushed tissues which can cause the precipitation and agglutination of blood flowing through or beside the crushed tissues?

2. Can the crushing of gross regions of the human body or of specific tissues or organs initiate processes which can change all the circulating blood to a sludge whose masses are large enough and rigid enough to retard the flow in small vessels enough to cause them to become anoxic and leak?

3. From crushing injuries alone, can the circulating blood be changed to a sludge which resists flow through small vessels enough to cause rapid local fluid losses all over the body, plugging of vessels with agglutinated masses, decreasing circulating blood volume, failure of venous return and death?

4. Following trauma, does rapid ingestion of coatings containing red cells by the phagocytes of liver, bone marrow and spleen (*a*) contribute to decreasing the total numbers of circulating red cells and (*b*) assist in causing progressively decreasing circulating blood volume?

5. In many injuries, hemorrhage and trauma are of course both present. Can these sludge mechanisms contribute to the decreased venous return in animals and human patients who have suffered combinations of hemorrhage and trauma?

These five questions define the broad outlines of the problem. Note that the questions deal with (*a*) concepts of chemical reactions, (*b*) concepts of degree and (*c*) concepts of rates. The rest of this paper is an attempt to find the beginnings of the answers to the first of these questions.

Reflections About the First General Question.—Consider the first general question in the aforementioned series. Obviously this question needs subdividing, for it contains or implies questions such as these:

Are the precipitation and agglutination of the blood flowing past the injury due to the liberation of one or more diffusible substances from injured tissues? Is the same diffusible substance released from each crushed tissue? What factors determine the rates of release of the diffusible substances? If such diffusible substances are released from injured tissues, do they always react and then become inactive at or very near the site of injury, or may they be carried in the circulating blood for a time and act later, after they have accumulated to or above some threshold concentration? That is, may some one or more of such diffusible substances act immediately and some accumulate in solution in the circulating blood for a time after an injury and later initiate changes in the mechanical consistency of the circulating blood?

These questions cannot at present be tested directly, but, as a first step in finding the answers to them, the following questions can be asked, each of which can be tested by direct methods.

(*a*) Which tissues or organs cause sludging of the blood after they are crushed?

(*b*) What are the characteristics of the sludge produced by the crushing of each tissue? Are the sludges thus produced alike or visibly different?

(*c*) How slight an injury causes sludging of the blood passing the injured area?

(*d*) What degree of severity of injury is present after tissue is crushed? What happens after each?

(*e*) For how long a time after a tissue is crushed does the sludging of the blood continue? What factors determine the duration of this process?

(*f*) What factors determine and limit the rates of production of sludge and the duration of the production of sludge after a mechanical injury?

II. Experimental Crushing of Mouse Striated Muscle.—The purpose of this experiment was to find the effects of slight trauma to a muscle.

An adult male mouse was anesthetized with 1.2 mg. of pentobarbital sodium in 0.4 cc. of water given subcutaneously. Its fur was then brushed lightly with a little petrolatum to (*a*) hold the ends of the hairs together to prevent cut hairs from being blown onto the exposed tissues and (*b*) to cause the animal to shed the Ringer solution escaping from illuminated areas. A cut was made with scissors through the skin transversely across the anterior abdominal wall about halfway between the xiphoid process and the symphysis pubis, and a midline incision led from this back toward the pubis. The skin retracted in all directions by its own elasticity, exposing a roughly triangular area of the lower abdominal musculature. During the cutting, the scissors were closed slowly, a procedure which crimps and thromboses small cut blood vessels, thus decreasing the number of small hemorrhages (Knisely, Bloch and Warner [34]). The cut edges of the skin were examined by reflected light at 32 diameters for clots and hemorrhages. One small arteriole had bled enough to yield a clot shaped like a doubly convex lens, about 2 mm. in diameter and 0.5 mm. thick; otherwise no blood was lost. The surface of the exposed abdominal musculature was then examined at 32 and 48 diameters to see whether the operation had initiated precipitation and agglutination of blood flowing through small vessels of the area. No sludge was seen, probably owing to our inexperience; many times since then we have seen sludging of the blood passing through some of the superficial vessels of such freshly exposed areas.

By cautery, a paramesial slit about 4 mm. long was made bloodlessly through one side of the exposed muscle. The quartz illuminator tip was then inserted through this slit and an area of striated muscle brightly transilluminated for microscopic study. The musculature of the lower anterior body wall was about 1 to 2 mm. thick. Thus this preparation provided several square centimeters of thin, nearly intact, living striated muscle for experiments.

The small vessels within the muscle itself, which are deeper than the superficial vessels and thus less exposed to injury during retraction of the skin, were then examined at 48 and 96 diameters for evidences of trauma; none were seen. The vessel pattern is that described in striated muscle by Spalteholz in 1888.[35] The blood flowing through the arterioles, capillaries and venules of the muscle was not agglutinated; the red cells were all free from each other; no white cells were sticking to vessel walls, nor did the walls exhibit any pathologic dilatations or sacculations. There was no visible hemocentration of the blood flowing through any of the vessels of this muscle, and no small hemorrhages, clots, thrombi or emboli were present in the muscle. These observations are the first controls for the following experiments.

Next, a small area of the muscle was traumatized as gently as could be done without special microdissection equipment. To do this, the illuminator tip was raised against the inner surface of the muscle and then the muscle directly over the tip was compressed and partly crushed with one firm wiping motion of a small, smooth, round-edged forceps handle. The injured area was about 3 mm. in diameter; the muscle was about 1 mm. thick at this point.

As noted, the injury was kept as slight as possible. When the forceps handle had passed, the muscle was not left crushed out of shape, as after the removal of a hemostat. As the pressure was removed, the muscle fibers assumed their normal cylindric shapes again; they showed no visible injuries at 96 diameters' magnification. The muscle was injured at 4:30 p. m. The injured area was then observed continuously for the duration of the experiment, four hours and ten minutes.

Results: Immediately after the trauma there were three clearly recognizable zones as follows:

1. Two postcapillary venules in the center of the injured area were plugged with a precipitated-agglutinated mass formed during the injury. No blood was passing through these vessels; hence they were not pouring sludged blood into the general circulation.

2. The afferent capillary ends of all other small venules in the injured area were receiving normally fluid blood, and precipitated-agglutinated (sludged) blood was flowing from their efferent ends into the next larger venules. The red cells could easily be seen agglutinating into firm masses as they passed through the venules in the damaged area. This was a very slight injury, yet all the blood flowing through the injured area was coming out as sludged blood. The sludged blood did not seem to flow much more than one fourth as fast as did the normal blood in vessels of comparable size in adjacent uninjured areas. White cells were sticking to the walls of those venules in the damaged area through which blood was flowing. Groups of them amassed and then broke loose and were carried downstream. Irregular dilatations, bulges and sacculations developed in the walls of injured vessels, but the walls did not weaken enough to permit diapedesis of red cells or hemorrhages (E. R. and E. L. Clark [10]).

3. The blood flowing through the vessels of the contiguous, untraumatized muscle and through untraumatized muscle in neighboring microscopic fields was as normal as before. (This is both an observation and a control.)

The sludge being formed in the slightly injured mouse muscle did not have the same consistency as that formed in the crushed monkey omentum; the clumps or red cells were smaller, more fragile and less sticky to each other than those formed in the monkey omentum.

35. Spalteholz, W.: Die Vertheilung der Blutgefässe im Muskel, Abhandl. d. math.-phys. Cl. d. k. sächs. Gesellsch. d. Wissensch. **14**:507, 1887-1888.

At 6 p. m., ninety minutes later, the following observations were made: 1. The plugs were still present in the two thrombosed venules. 2. The damaged area was still pouring sludged blood into the smaller veins which drained it. A point was found where a venule which came from the damaged area joined one which came from an area of undamaged muscle. Here the experiment and the control were present in one microscope field; it was easy to compare the sludged and the normal blood. There were no free individual cells in the blood passing out of the venule draining the damaged area; all this blood was precipitated and agglutinated into a sludge. 3. No two red cells were sticking together in the blood from the uninjured area; all were free, each turned over by itself unattached to any other—that is, normal blood was flowing through normal vessels in adjacent untraumatized areas of the muscle.

At 6:15 p. m. blood passing through the injured area was still changing to a sludge. At this time, however, there began to be a change. Some of the smallest venules in the injured area had almost normal blood for a few minutes and then sludged blood again. The sludge was being formed intermittently, and the sludge being formed was softer, i. e., the clumps had a fluffy, feathery character rather than a firm, rigid texture. The area was still pouring sludge into the venous system, but there had been a definite decrease in rate of production of sludge, and that produced might better be called a "slush" than a sludge.

It seems reasonable to assume that whatever had been initiating the production of sludge was not reaching or acting in the blood flowing through the injured area as rapidly as during the first ninety minutes after injury.

At 6:30 p. m. the following observations were made. 1. The plugs were still present in the two thrombosed venules. 2. The blood flowing through the injured area was still changing consistency. The sludge formed was less pasty than that formed at first. It was softer, the clumps were more plastic and the rates of flow through these vessels were increasing, approaching the rates through vessels of similar size in the neighboring undamaged areas. The walls of the venules in the injured area were lined with sheets of white cells all rolling along the inner surfaces of the endothelium (E. R. and E. L. Clark [10]). It seemed probable that this injured area would not form sludge much longer. 3. Normal, unagglutinated blood was coming from the uninjured areas.

At 7:30, three hours after the injury, these observations were noted: 1. The two venules originally thrombosed were still plugged up. 2. Patches of slightly agglutinated blood were forming at irregular intervals in blood flowing through the injured area. 3. Normal blood was coming out of the uninjured areas.

At 7:40 the same area was retraumatized by one light wiping stroke of the forceps handle. Immediately the blood flowing through the area became thick and pasty again. This shows that the substances which initiate sludge formation, or their precursors, were not all gone from the injured area.

At 7:55 p. m. the following observations were made: 1. Thrombosed vessels were still thrombosed. 2. Blood flowing through the injured area was still changing to a stiff sludge. 3. Normal blood was coming out of venules of neighboring uninjured muscle.

At 8:15 p. m. there was no change.

At 8:40 p. m. these observations were made: 1. Thrombosed vessels were still thrombosed. 2. All the blood flowing through the injured area was changing to a sludge and passing into the venous system. 3. Normal blood was coming from uninjured areas. The experiment was discontinued.

Summary of This Experiment with Crushed Mouse Muscle.—1. A light injury to mouse striated muscle caused precipitation and agglutination of the blood flowing through the injured area. Crush and flow through the crushed muscle were both necessary, and the two together were sufficient to produce a flow of sludged blood into the general circulation.

2. The precipitate was probably being formed in less than half a second.

3. For about one and three-fourths hours after the injury, the rate at which sludged blood was poured into the venous system was as fast as the rate of flow through the crushed area.

4. For the next one and one-fourth hours a progressively decreasing fraction of the blood flowing through this area changed consistency.

5. The clumps formed in the first period were fairly tough and rigid; those formed in the second period were increasingly plastic, flexible and fragile.

6. The visible sludge formed rapidly before the blood left the field being observed. This observation does not mean that all the sludge initiator substances reacted and became inactive within the microscope fields observed. Initiator substances which might be able to cause changes in the blood at some later time and distant place

may have been carried out of sight into the general circulation.

7. Retraumatization of the area reinitiated the formation of rather rigid clumps. This shows that the precursors of the initiator substances or the initiator substances themselves were not all gone from the area at the end of three hours, and it strongly suggests (*a*) that traumatized men should not be moved any more than necessary and (*b*) that when necessary to move them they should be moved as gently as possible to minimize the reinitiation of release of sludge initiator substances from previously traumatized tissues.

8. After retraumatization, the area poured sludged blood into the venous system for at least an hour.

9. The foregoing reactions occurred—hence can take place—in the absence of diapedesis of red cells or of hemorrhages or local hemoconcentrations and fluid loss at the sites of injury.

COMMENT

One experiment with crushed monkey omentum and one with crushed mouse striated muscle have now been described in detail.

In many other experiments on mice, larger single areas of striated muscle have been crushed and areas have been subjected to harder crushing, the most severe consisting in clamping a mosquito hemostat onto an area so tightly that on its removal the mashed muscle retained the impressions of the instrument's jaws and no blood flowed through the crushed area again.

The intestines of mice have also been crushed, sometimes lightly, sometimes more heavily. After all such injuries to the striated muscles and to the smooth muscle walls of the intestines of mice, three regions of each injury may be distinguished:

1. A region in which the small vessels are thrombosed. This region may be of any size, depending on the size of the instruments between which the tissue is traumatized and the force with which the tissue is crushed. This region pours no sludge into the venous system so long as its vessels are thrombosed.

2. A region at the side of or surrounding the first, a partially crushed region, in which the tissue is injured but through which blood is still flowing. This partially crushed region may be called the "sludging zone." Each small venule of this region pours sludged blood into the venous system.

3. A region at the side of or surrounding the partially crushed sludging zone in which the tissues have not been injured enough to cause precipitation and agglutination of the blood flowing through them.

These regions are present in tissues which have been injured enough to cause transudation of plasma, diapedesis of red cells and hemorrhages (E. R. and E. L. Clark [10] and Phemister [36]), as well as in areas with lesser injuries.

Very slight injuries may have very small thrombosed zones. Heavier injuries have larger thrombosed regions. After delicate mouse muscle has been clamped with a strong hemostat and the hemostat then removed, the crushed and thrombosed zone is as large as the area of the jaw of the hemostat and the partially crushed sludging zone around it frequently is very narrow.[37] When a simple hard crush is made with a small hemispherical instrument, the thrombosed region is in or near the center of the crushed area, the sludging zone surrounds this and normal-appearing muscle containing normally flowing blood surrounds the sludging zone.

The edges of laparotomy incisions have been examined in many mice and in several rhesus monkeys. The sludging of blood passing in close proximity to the edges of laparotomy incisions can be seen wherever the tissues can be transilluminated and a microscope focused on the small vessels. All along each edge of each incision is a thrombosed zone. The cut and crimped ends of vessels are thrombosed. But where small vessels pass in close proximity to the injured tissue or through the injured tissue, the blood changes to a sludge as it passes through them. The tags of tissue at the edges of jagged laparotomy incisions often contain high proportions of partially crushed tissue.

When striated or smooth muscle is crushed with irregular objects or when multiple small crushes are made, thrombosed areas, partially crushed sludging zones and normal areas are all present, intermingled in various patterns. All the injuries we have studied have had each of the three zones. The degree of crush and the

36. Phemister, D. B.: The Mechanism and Management of Surgical Shock, J. A. M. A. **127:** 1109 (April 28) 1945.

37. Advantage is now being taken of this fact in designing surgical technics for laboratory experiments. By using clamping and cutting procedures which keep the sludging zones very narrow, laparotomies can be performed in mice and monkeys without causing any microscopically detectable change in the consistency of the blood flowing through the eye vessels. So little sludge is produced that it does not appear in the general circulation in detectable amounts (Knisely, Stratman-Thomas, Eliot and Bloch [6] and Knisely, Bloch and Warner [24]).

pattern of the injury determine (*a*) the total volume of injured tissue and (*b*) the relative proportions of the thrombosed and partially crushed or sludging zones.

The amount of partially crushed tissue varies from injury to injury, but in each case it is the partially crushed tissue which pours sludge into the venous system. The amount of such partially crushed tissue present after an injury depends on the size and shape of the instrument, on the pressure applied and on the size and shape of the structures which supported the injured tissues.

From these observations, it seems probable that when they are crushed striated and smooth muscles release substances capable of diffusing in through the vessel walls and reacting with constituents of the blood flowing through the patent vessels.

From the observations it seems probable that the maximum amounts of initiator substances reach the blood from partly crushed tissue, that is, from regions injured enough to release the initiator substances but not injured enough to thrombose the enclosed vessels. The edge of a thrombosed region may of course be contributing initiator substances to a contiguous partly crushed region.

The sludge formed at the site of the injury is formed rapidly, before the blood leaves the field being observed, but this does not mean that all the sludge formed necessarily is formed at the site of the injury. Excess initiator substances which might be able to cause changes in the blood at some later time and distant place may well be being carried out of view into the general circulation. The observations reported thus far were made in mammals, but some observations made in amphibians (frogs and salamanders) may have a bearing on this point. In these animals an extensive operation done with care to prevent loss of blood (Knisely, Bloch and Warner [24]), but without care to prevent partial crushing of tissues at the edges of incisions, is often followed by a slow increase in the viscosity of the plasma of all the circulating blood. In these animals a visible sludge may or may not form at the sites of injury. It seems reasonable to assume that in these amphibians initiator substances are carried into the general circulation before producing a visible change in the blood. Hence, by analogy it seems possible that in mammals excess initiator substances released at the sites of injury are being carried out of view into the general circulation. Such substances could cause further changes in the circulating blood and/or help bind masses of sludge together into larger masses whenever they accumulate to or above some threshold concentration. This is not altogether an academic speculation; it may have a practical aspect, for transfusions given animals or men during or after the accumulation of such substances in the circulating blood must, among other things, dilute the initiator substances.

It seems reasonable to suspect that the initiator substances might be related to the substances capable of initiating blood clotting. If this is true, then sludge initiator substances should be released from many different injured tissues and organs of vertebrates.

The outer surfaces of the erythrocyte-containing masses formed in blood flowing through crushed tissues are not conspicuously different either in appearance or in observed behavior from the coated, red cell–containing masses formed in monkeys with P. knowlesi malaria. Hence, (*a*) the P. knowlesi malaria precipitates should be examined both chemically and immunologically to determine whether they are monkey fibrin or related to fibrin and (*b*) the precipitated coatings with their contained red cells formed in blood flowing through crushed tissues may be ingestible by phagocytes of spleen, bone marrow and liver. In monkeys with malaria, this mechanism destroys blood rapidly (Knisely, Stratman-Thomas, Eliot and Bloch [6]). Thus the phagocytosis of coated red cells may well contribute to the removal of blood from the vascular system after a traumatizing injury and to the anemia which not infrequently follows operations (Knisely, Bloch and Warner [24]).

A bit of sludge can reach the general circulation only by being carried into the venous system. Hence sludged blood can come from one minute injured area into the general circulation no faster than the flow through the venules which drain the injured area. These facts are important when one is considering the mechanisms of the crush syndrome (review and bibliography by Bywaters [38]).

The volume of sludge produced by the partially crushed area drained by one small venule may be expressed as the summation of volumetric rates of flow through the venule during the periods while sludge is produced. Hence, by induction, the amount of sludge produced by any partially crushed area is equal to the summation

38. Bywaters, E. L. G.: Ischemic Muscle Necrosis: Crushing Injury, Traumatic Edema, the Crush Syndrome, Traumatic Anuria, Compression Syndrome; a Type of Injury Seen in Air Raid Casualties Following Burial Beneath Debris, J. A. M. A. **124**:1103 (April 15) 1944.

of the amounts produced in each small venule of the area through which blood is flowing. Thus after injury the rate at which sludged blood is poured into the general circulation should be a result of (*a*) the volume of the partially crushed tissue and (*b*) the rates of flow of blood from the partially crushed area into the venous system. The total amount of sludge produced should be the result of these two factors and (*c*) the duration of the periods during which the sludge is produced by the injured area.

The amount of coated agglutinated blood cells (sludge) in the vascular system at any time must be equal to the amount produced up to that time minus the amount removed or destroyed or resolved into normal blood. More usefully expressed, the amount of sludge in the vascular system at any moment must be equal to the summations of the rates of production minus the summations of the rates of removal, destruction and disintegration up to that moment. Thus sludged blood should accumulate within the vascular system during the periods when the rates of production are greater than the rates of removal and resolution. If one injury or a group or series of injuries were large enough and the flow through their sludging zones fast enough, it should be possible to change all the circulating blood to a thick, mucklike sludge (Knisely and Bloch [4b]).

Microscopic studies are now an indispensible part of macroscopic studies of the circulatory system. At present it is not possible to determine with certainty by means of any known sign, symptom, blood pressure reading, kymograph record, sedimentation rate determination or other macroscopic indicator or by examination of histologic sections whether an experimental animal has, or has had, precipitated-agglutinated blood. Consequently, (*a*) it is not now possible to know that the blood was not precipitated and agglutinated to a circulating sludge in any previous experiment involving traumatic injuries and (*b*) it is not possible to carry out analytic experiments to determine the mechanisms operating in traumatic and other forms of shock or to determine the mechanisms operating in other experimental pathologic conditions without having continuous or closely spaced microscopic observations of the circulating blood as controls to determine whether and to what degree precipitation and agglutination of the blood is a part of the induced pathologic change. The "eye method" outlined in the methods section of this paper permits microscopic control of many types of gross physiology experiments.

The study of blood flowing past a minute local lesion may be useful for finding the sources of the substances which precipitate and agglutinate the blood in other pathologic conditions and diseases. Sludges, having various physical characteristics, have now been seen in human patients with diagnoses of about forty different pathologic conditions and diseases (Knisely and Bloch [4]). In each of these, the sources of the initiator substances must be found. Microscopic study of blood flowing past minute local lesions is one method of hunting for the sites of production of initiator substances. The technic should be used to study (*a*) small thermal burns, (*b*) small radium burns, (*c*) small roentgen ray burns, (*d*) small lesions caused by various chemicals, (*e*) small lesions of tuberculosis in experimental animals, (*f*) small areas inoculated through microneedles with various bacteria, (*g*) small neoplasms of all the kinds which can be obtained in experimental animals, (*h*) the sites of development of extraerythrocytic plasmodia in the malarias in which these occur and (*i*) the points of attachment of hookworms, trichina cysts, liver flukes and other parasites. New toxic substances or previously unknown effects of previously known toxins may be found (Youngner and Nungester [39]). The point is to get to the site of the lesion in vivo with adequate operative technics, light, temperature control and lenses.

SUMMARY AND CONCLUSIONS

For distribution of emphasis, the summary and conclusions is divided into sections on controls, methods and results of crushing injuries.

I. Controls.—1. The blood coming down the arterioles of each tissue is a statistically valid sample of all the flowing arterial blood in the body.

2. Most of the time, under most conditions, nearly all the circulating blood must, because of the anatomy and the dimensions of the living vascular system, pass through vessels having an internal diameter from about once to twice or at most three times that of the red cells on every trip around the circulatory system.

3. In normal animals and men the blood cells are not agglutinated, the red cells repel each other slightly and the white cells do not stick to vessel walls. The walls of capillaries, post-

39. Youngner, J. S., and Nungester, W. J.: Effect of Type III Pneumococcus Polysaccharide and Gelatin on Circulation and Sedimentation Rate of Erythrocytes in Mice, J. Infect. Dis. **74**:247 (May-June) 1944.

capillary venules and venules do not leak enough to be detected by microscopic observation.

4. Pentobarbital sodium in anesthetic doses does not cause intravascular agglutination of the circulating blood of Macaccus rhesus monkeys.

5. Neither pentobarbital sodium nor sodium amytal in anesthetic doses causes intravascular agglutination of the circulating blood of mice.

6. No single factor or combination of factors of the anesthetics used, the withdrawing of the monkey omentum or the brilliant transillumination of tissues whose temperatures are maintained at normal has caused intravascular agglutination of the blood.

7. Laparotomies can be done with sufficient care to prevent general precipitation and agglutination of all the circulating blood.

8. With routine care, normal monkeys have been kept under pentobarbital sodium anesthesia and the circulation in abdominal viscera observed with microscopes without causing general intravascular agglutination of the blood or visible pathologic changes in the walls of small blood vessels for as long as fourteen to eighteen hours.

II. Methods.—1. A method is described for maintaining controlled pentobarbital sodium anesthesia of monkeys by intrapleural injections; this is useful for making microscopic observations of abdominal structures.

2. Simple methods are described for studying the vessels and blood of the eyelid, nictitating membrane and bulbar conjunctiva of experimental animals not operated on and of those operated on. The methods have three obvious uses:

(*a*) To assist in preselecting normal animals for experiments. As agglutinated blood is not normal, as agglutinated blood has already been found as a part of the pathologic change in about forty human diseases and as many of the organisms which affect human beings also affect experimental animals, microscopic observations of the blood and vessel walls are a necessary part of the preselection of normal animals for experiments.

(*b*) To make continuous observations during the course of experiments on intact animals not operated on to determine the effects of various agents and procedures on the circulating blood and local vessel walls.

(*c*) To make continuous observations as controls to be certain that during experiments designed with the intention of studying normal animals no agent or procedure is causing mechanical changes in blood and/or pathologic changes in vessel walls.

3. A method is described for studying the blood passing through vessels in or near a minute local lesion. The method should be useful for studying the blood passing through or near lesions caused by many different agents.

III. Results of Crushing Injuries.—1. After a crushing injury to monkey omentum, smooth muscle of mouse intestine or striated muscle of a mouse, three zones may be distinguished: (*a*) a thrombosed zone, (*b*) a partially crushed or sludging zone and (*c*) a zone which is injured so little that the blood flowing through it undergoes no detectable change.

(Pentobarbital sodium in monkeys and mice and sodium amytal in mice do not in anesthetic doses prevent the precipitation-agglutination of blood flowing through a crushed area.)

Seen as possible initiating factors in traumatic shock, the observations made in these tissues may be summarized as follows:

2. Crushing plus flow through a vessel in the crushed area yields a stream of sludge into the general circulation.

3. Crushing plus thrombosis of a crushed vessel yields no sludge to the venous system.

4. Flow without crush yields no sludge.

5. Thus, after trauma, (*a*) local crush plus (*b*) flow through a vessel in the crushed area are both necessary and, together, sufficient to yield a flow of sludged blood into the general circulation.

6. After crush, precipitates can form around or between the moving blood cells in less than a second, while the blood is moving less than a millimeter.

7. It seems reasonable to suspect that the sludge initiator substances might be related to the substances capable of initiating blood clotting. If this is true, then many tissues and organs of vertebrates should release such substances when they are injured.

8. At no time can sludged blood pass into the venous system faster than the flow through the crushed tissue.

9. For a time after the crush, the rate at which sludge is poured into the venous system can be as fast as the rate of flow through an open vessel in the crushed area.

10. Retraumatization of an area can reinitiate sludge formation in blood flowing through the area.

11. This sludge can be formed in an area from which or into which there is (*a*) no hemorrhage and (*b*) but little loss of plasma through injured vessel walls.

12. This sludge is also formed in the partially crushed regions of areas injured severely enough to cause local transudation of plasma, diapedesis of red cells and/or hemorrhages through walls of injured local vessels.

13. When first formed, some of the masses have sufficient internal rigidity to bulge the walls of the vessel through which they are being forced; if not changed, such masses would resist passage through capillaries.

14. When first formed, the outer surfaces of the precipitated material is sticky to itself; hence, if not changed, such masses must, whenever they touch each other, tend to stick together and form larger masses.

15. The outer surfaces of the red cell–containing masses formed in blood flowing through crushed tissues are not visibly different in appearance or in observed behavior from the coated red cell masses formed in monkeys with P. knowlesi malaria.

16. Hence, the precipitated coatings with contained red cells formed in blood flowing through crushed tissues may be ingestible by phagocytes of spleen, bone marrow and liver. In monkeys with malaria, this mechanism destroys blood rapidly.

17. During periods when the rates of production of sludge are faster than the rates of removal and/or the resolution of sludge, sludged blood should accumulate under the vascular system. If one injury or a group or a series of injuries were large enough and the flow through their sludging zones fast enough, all the circulating blood should should change to a thick, mucklike sludge.

One of our problems consists in attempting to present material which can be recorded only in motion pictures in conventional published form. A single frame from a motion picture seldom contains sharp enough detail for publication as a still picture, and no still photograph records or gives the impression of continuous processes. The figure in this paper was designed to retain in sharp accuracy the dimensions of the living stationary structures and, in addition, give an impression of the rapid movement of the vessel contents. The figure was made by Dock Curtis, artist and medical student, amid a general feeling that it could not be done.

A NEW TREATMENT FOR POSTOPERATIVE PULMONARY COLLAPSE

E. H. GRANDSTAFF, M.D.
Director of Anesthesia, Kansas City General Hospital
KANSAS CITY, MO.

Of all the complications following surgical procedures, those involving the lungs are among the most feared and the most commonly reported.[1] The incidence of atelectasis has been variously reported as causing from 3 to 70 per cent of all postoperative complications, with 40 per cent mortality among the persons affected.[2] In operations of the upper part of the abdomen the morbidity from respiratory complications is said to be about 10 per cent.[2] At the Kansas City General Hospital during two years in which careful records have been kept, the incidence of morbidity and mortality from respiratory complications is seen to be much lower (tables 1 and 2).[3]

All patients with atelectasis and massive pulmonary collapse in this series recovered speedily. Pneumonia was named as the cause of death or was associated with other causes in 24 of 125 postoperative deaths. In most cases the pneumonia occurred as a terminal process a number of days following operation and was associated with carcinomatosis, peritonitis, nephritis and other serious conditions. The apparently larger number of deaths following the use of cyclopropane is due to the fact that this is the anesthetic of choice at this hospital for patients who present a bad risk and for patients undergoing long and shocking operations. It is felt that it is the safest agent to give these patients in serious condition on account of the rapid recovery period with the lower incidence of postoperative complications of all types,[3] the high percentage of oxygen which it is possible to give during the administration of the anesthetic and the lack of injury to the liver or kidneys or of other pathologic damage. Many of these patients

TABLE 1.—*Results in Cases in Which Anesthetic Was Used*

	Number of Cases	Respiratory Complications, Number of Cases			Respiratory Complications, %	Mortality, Number of Cases			Respiratory Complications, %		
		Collapse	Atelectasis	Pneumonia		Collapse	Atelectasis	Pneumonia	Collapse	Atelectasis	Pneumonia
Spinal	718	2	7	14	3.1	0	0	0	0.28	0.9	1.8
Cyclopropane	816	0	2	13	1.6	0	0	1	0	0.27	1.6
Ether (open drop)	275	2	3	5	3.2	0	0	1	0.73	1.09	1.8
Nitrous oxide-ether	19	1	0	10	57.9	0	0	2	5.3	0	52.6
Cyclopropane-ether	100	2	3	3	8.0	0	0	1	2.0	3	3
Nitrous oxide	136	0	0	3	2.3	0	0	2	0	0	2.3
Pentothal sodium	538	0	0	0	0	0	0	0	0	0	0
Spinal-gas	102	0	0	3	3.0	0	0	3	0	0	3.0
Total	2,704	6	15	51	2.6	0	0	24	0.22	0.55	1.8

To summarize this table, in 0.22 per cent of all cases in which an anesthetic was used there was massive collapse of the lungs; in 0.55 per cent atelectasis and in 1.8 per cent pneumonia, with an ultimate mortality of 0.88 per cent for all cases in which an anesthetic was used (33 per cent of the total morbidity from disease of the respiratory tract.)

TABLE 2.—*Percentage of All Cases Having Postoperative Complications*

	Drop Ether, %	Cyclopropane, %	Spinal, %	Nitrous Oxide, %	Pentothol Sodium, %
Nausea and emesis	47	28	17	15	11
Distention	8	8	10.9	2	0
Catheterization and retention	21	14	15	18	4
Tachycardia	32	18	20.5	11	5.8
Pneumonia	1.8	1.7	2.0	2.0	0
Atelectasis	1.09	0.27	0.9	0	0
Massive collapse	0.73	0	0.28	0	0
Fall in blood pressure without shock	3.8	3.4	1.0	4.0	0
Shock	5.0	1.4	2.0	0	0
Headache	5.0	6.0	5.7	0	2.2
Other complications, as wound infection, neuritis, cough, irrational, embolism, etc.	5.0	10.0	25.7	8	5.3

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1. Adams, W. E.: Thoracic Surgery: Postoperative Pulmonary Atelectasis, Am. J. Surg. **56**:180-191 (April) 1942.

2. Elkin, D. C.: Postoperative Pulmonary Complications, Surg., Gynec. & Obst. **70**:491-493 (Feb.) 1940.

3. Grandstaff, E. H., and Schaerrer, W. C.: Progress in the Anesthetic Department of the Kansas City General Hospital, 1940, J. Missouri M. A. **38**:352-353 (Oct.) 1941.

already had nephritis, peritonitis, pathologic conditions of the lung or cardiac decompensation, and the morbidity and mortality from respiratory complications in these cases cannot be considered as primarily due to the anesthetic agent. At the other extreme, ether is not given at this hospital, exclusive of operations on ear, nose and throat, except to patients who are in excellent condition. The more frequent respiratory complications following the use of ether, either by itself or in combination with one of the gases, are thus due directly to the anesthetic agent, because of its irritating effect on the lung tissue, with stimulation of bronchial secretions, production of a high percentage of nausea and vomiting, with attendant danger of aspiration, and a long recovery period with depressed respiration.

There have been many suggestions as to the cause of postoperative collapse.[4] It is most likely to occur after operations high in the abdomen from splinting of the lower intercostal muscles or from pain, resulting in diminished aeration, and stagnation of mucous secretions.[5] Pain from the incision in operations on the abdomen has been found to cause a 59 per cent depression of vital capacity by a reflex inhibition of respiration.[6] When following operation on a kidney, the collapse and atelectasis always occur on the opposite side from the operative site, probably because of interference with respirations by the elevation of the kidney rest and by accumulation of secretions on the dependent side. This is the case in the present series, with massive collapse of the left lung on the third day following a nephrectomy on the right side (case 1).

Any patient with severe oral sepsis, chronic bronchitis or acute or chronic infection of the respiratory tract should be regarded as a possible candidate for postoperative collapse and given special treatment to attempt to prevent it.[1] Most of the patients in this series who had a severe degree of pulmonary collapse had a pronounced oral sepsis.

Excessive postoperative sedation should be avoided, as this raises the threshold of stimulation of the cough reflex by accumulated secretions. Atropine or scopolamine should not be administered postoperatively, as it merely inspissates the mucous secretion and prevents the patient from coughing it up. A tight binder or severe abdominal or bladder distention will reduce the vital capacity and allow stagnation and accumulation of secretions. Preoperative sedation should not be excessive, as this, together with the use of cyclopropane, will seriously depress the respiration and allow congestion and accumulation of secretions during a long operation under deep anesthesia. Atropine and scopolamine should not be given immediately preceding the anesthetic, but there should be an interval of about forty-five minutes, at the end of which time these drugs reach their maximum anhidrotic effect. If given and followed immediately by the anesthetic, an excess of mucus will be formed owing to the effect of the anesthetic before the drugs have had time to reach their full effectiveness. Then later this mucus which has been formed during the first few minutes of the anesthetic will be dried and remain in the bronchioles as a plug.[4a] This is well illustrated by case 3, in which scopolamine was administered and the cyclopropane-ether anesthetic started immediately, the preceding operation having been canceled and the surgeon being in an uncooperative mood and stating that it made no difference when the premedication was given. Massive collapse of the lung followed twenty-three hours later.

The type of anesthetic appears to have more significance in this series than is usually attributed to it. Pulmonary complications followed 3.2 per cent of the inductions of anesthesia with ether by the open drop method. Complications following 3.1 per cent of the inductions of spinal anesthesia may be due to the paralysis of the lower intercostal muscles in the case of high spinal anesthesia.[5] However, in this series, complications occurred just as frequently after the use of low spinal anesthesia. Postoperative position, especially for old people, is considered as more contributory than the average spinal anesthetic, as the paralysis of the intercostal muscle produced by spinal anesthesia is worn away within four hours, except after use of nupercaine hydrochloride or continuous spinal anesthesia.[5]

Most interesting is the finding that ether combined with oxygen following induction of anesthesia by nitrous oxide or cyclopropane produces a prohibitively high percentage of respiratory complications. This is due to the great irritation by the ether of the bronchial mucosa, causing

4. (*a*) McCall, J. W., and Freeman, M. S.: Postoperative Atelectasis: Presentation of Four Cases, Ohio State M. J. **38**:546-550 (June) 1942. (*b*) Moore, A. E.: The Treatment of Postoperative Pulmonary Atelectasis, Surgery **5**:420-435 (March) 1939. (*c*) Gius, J. A.: Postoperative Atelectasis and Related Pulmonary Complications: Collective Review, Internat. Abstr. Surg. **71**:65-78, 1940; in Surg., Gynec. & Obst., July 1940. (*d*) Adams.[1]

5. Marshall, J. M.: Postoperative Pulmonary Atelectasis, U. S. Nav. M. Bull. **42**:601-606 (March) 1944.

6. Coller, F. A., and Singleton, A. O.: Postoperative Complications, South. Surgeon **11**:560-573 (Aug.) 1942.

mucus and obstruction; the high percentage of oxygen in this inspired closed ether atmosphere allows its almost immediate removal by the blood stream, leaving a collapsed lung behind one or numerous small obstructive masses of mucus.

Cyclopropane was followed by the fewest pulmonary complications as well as other types of complications, in spite of the fact that it is administered to those patients already extremely ill but requiring operation. It causes a negligible amount of bronchial irritation and production of mucus. In a few cases collapse follows administration of cyclopropane, particularly when combined with a large dose of morphine, because of the depression of the respiration from the removal of the carbon dioxide to produce purposely a shallow respiration and a quiet abdomen for surgical intervention.

Aspiration of blood or vomitus during or after operation is an important consideration also, as this may plug the bronchioles. If the airway does not seem to be perfectly clear at the end of operation, this aspiration should be done before the patient is removed to the ward.

The onset of pulmonary collapse occurs suddenly, usually during the first three days, with pain in the chest, dyspnea and a sharp rise in temperature and in pulse and respiration rates. The patient is usually found sitting up in bed, anxious, dyspneic and cyanotic. There is more or less fixation of the affected side, with dulness on percussion, absence of breath sounds, elevation of the diaphragm and shift of the area of cardiac dulness toward the affected side. The unaffected side is hyperresonant, and there are increased breath sounds.[4a] The sputum is scanty at first but quickly becomes abundant and mucopurulent. The white blood cell count may be 15,000 to 20,000. The roentgenogram is characteristic, with elevation of the diaphragm on the affected side, narrowing of the intercostal spaces and deviation of the heart and other mediastinal structures to the affected side, the lung appearing dense and homogenous.

Treatment of such collapse is, of course, primarily prophylactic. As soon as the operative schedule is posted for the following day, the intern on the anesthesia service and I exmaine each patient and plan the type of anesthetic which will be the best, considering the pathologic condition of the patient, the type of operation proposed and the use of cautery or roentgen ray equipment. A member of the anesthesia department then writes orders for the preoperative medication, giving a small dose of morphine for all patients except those who are young and vigorous. By small dose is meant 1/16 grain (0.0037 Gm.) to 1/8 grain (0.007 Gm.) for those above 50 years, 1/8 grain to 1/6 grain (0.01 Gm.) for those from 50 to about 25 years and 1/6 grain for those in good condition, in their twenties and thirties. Occasionally 1/4 grain (0.015 Gm.) is given in this group. Scopolamine is given in combination with the morphine preceding spinal anesthesia for further sedation, 1/150 grain (0.0004 Gm.) to 1/300 grain (0.0002 Gm.) being given with increasing age. Atropine is given preceding an anesthetic administered intravenously, as it has been found that there is more likely to be a fall in blood pressure during the administration of pentothal sodium if it has been preceded by the use of scopolamine. Atropine is also given to young children in preference to scopolamine, which rather seriously depresses them. Administration of the anesthetic is refused until the patient has received atropine or scopolamine for the proper interval previous to operation. Barbiturates are given to all patients preceding use of caudal, epidural or spinal anesthesia to avoid procaine reactions through depression of the central nervous system from stimulation of procaine and its derivatives. Barbiturates are given to those patients to receive nitrous oxide anesthesia to depress the metabolism further, which is necessary when administering this weak gas. They are also given preceding use of cyclopropane to decrease vagal tone and prevent cardiac arrhythmia from the combination of morphine and cyclopropane.[7] Ortal sodium is given to older people, over 50, and pentobarbital sodium in one or two 1.5 grain (0.009 Gm.) doses to younger patients. Seconal when combined with even a small dose of scopolamine has been found to be too depressing to the respirations of old people. Morphine and barbiturates are not given preceding tribromoethanol, as this combination produces severe respiratory depression. At the close of the anesthesia, an attempt is made to have the patient partially awake and to have his pharyngeal reflex back. Nitrous oxide is given during the last few minutes of cyclopropane anesthesia in order to fill the lungs with a substance which is much more slowly absorbed in case a portion of the lung should be cut off behind a mucus plug. Nitrous oxide requires several hours to be dissolved by the blood stream, while cyclopropane and oxygen are removed in a few minutes and in that case would leave a portion of lung collapsed in a short time. I have not seen a case of atelectasis develop after this

7. Robbins, B. H.; Baxter, J. H., and Fitzhugh, O. G.: The Use of Barbiturates in Preventing Cardiac Irregularities Under Cyclopropane or Morphine and Cyclopropane Anesthesia, Ann. Surg. **110**:84-93 (July) 1939.

precaution, even when operation is done high in the abdomen. Use of one of the elastic adhesives has been found useful in dressing wounds high in the abdomen snugly and yet allowing expansion of the chest.

When the patient is removed to the ward, he is placed at once on the side opposite to that on which he has been operated, the theory being that if the lung on the opposite side is constricted slightly by his weight there will be a compensatory expansion of the lung on the operated side and stimulation of deeper respiration with not so much splinting of the chest. After this, the position is changed from one side to the other every hour [4b] when the patient is not receiving intravenous infusions. No patient is to be placed in bed on his back and left there quietly indefinitely. The first day, inhalations of carbon dioxide and oxygen are given for two minutes out of every hour and the second day out of every two hours. The patients are then urged to take ten deep breaths voluntarily every hour. Postoperative sedation is held at a minimum, and no atropine or scopolamine is given. Because these measures have been followed, there has not been a case of massive collapse at this hospital in two years and only a few cases of mild atelectasis, which cleared up promptly with little special treatment.

If, in spite of these precautions, pulmonary atelectasis or collapse develops, the patient should be placed on the unaffected side in a moderate Trendelenburg position. He should be instructed to cough, with some one holding his abdomen, if the condition follows an operation on the abdomen, to give support to the abdominal wall and decrease the pain of coughing. A tight scultetus binder may be used to give abdominal support for a short time. Striking the patient on the back over the affected lung while encouraging him to cough will often help to dislodge the plug.[4b]

A new treatment consisting merely in cocainizing the throat with 5 to 10 per cent cocaine solution has been used in a number of cases, with spectacular results and almost instant cure in many cases (see cases 4 and 5 for roentgen demonstration). The cocaine solution in a cotton ball held in a curved applicator is placed far back in the throat and into the pyriform sinuses as if in preparation for a bronchoscopy. It has been found that the use of this procedure apparently relaxes the musculature of the bronchial tree enough that within a few minutes the patient will cough up a large plug of mucus and be relieved at once. Use of a little solution of epinephrine in the same cotton pledget will help stimulate the cough reflex. The patient is encouraged to cough, with some one giving support to the abdomen. This relaxing effect from the cocaine is thought to be the essential part of the procedure. Merely applying a cotton ball moistened with isotonic solution of sodium chloride or solution of epinephrine by itself to the back of the throat to produce hard coughing will not produce the desired effect. Application of the cocaine is followed by expulsion of the obstructing plug and dramatic relief in many cases.

During the next twenty-four hours or more, use of intermittent inhalation of oxygen and carbon dioxide is continued, to keep respirations deep and to attempt to reexpand all bronchioles. Chemotherapy with sulfathiazole or sulfadiazine is begun and continued for twenty-four hours or longer to prevent pneumonia from beginning in the congested and airless area.[1] The patient is rolled from one side to another frequently and made to continue to cough and take deep breaths. A set of blow bottles has been devised so that the patient can blow the water from one bottle into the other every hour; this helps increase and maintain expansion of the lung tissue.

There have been no failures from use of this method of cure of pulmonary collapse merely by cocainization of the throat. It has not been necessary in this hospital to resort to use of bronchoscopy, with its production of additional strain on the abdominal incision and great discomfort of the patient, since we have been using these measures.

REPORT OF CASES

CASE 1.—M. H., a fairly well nourished woman 33 years old, was brought to surgery October 31 for a nephrectomy on the right side on account of a complaint of severe pain in the right side and back, with discovery on the intravenous pyelogram of a large branching calculus in the right renal pelvis. Other history is noncontributory except for a chronic cough, and physical examination showed nothing significant. Phenolsulfonphthalein was excreted at a rate of 12.5 per cent on the right side and 37.5 per cent on the left side in two hours. The urine was loaded with white blood cells, with a heavy trace of albumin. Wassermann and Kahn tests of the blood elicited negative reactions. The sugar content was 88 mg., the nonprotein nitrogen level 28.5 mg. and the creatinine content 1.5 mg. per hundred cubic centimeters. The hemoglobin content was 10 per cent and the white blood cell count 6,600. The sedimentation rate was 17 mm. A mixture of 75 mg. of procaine hydrochloride crystals and 12 mg. of tetracaine hydrochloride in solution were administered in the first lumbar space; removal of a large rough kidney was accomplished without incident in an operation lasting sixty-six minutes, and the patient was returned to the ward in good condition. On November 1, terpin hydrate with codeine was given for the cough, with ammonium chloride and continuous inhalations of steam. Morphine, ¼ grain (0.015 Gm.), was given only once. On November 2 (Sunday) the patient was complaining of dysp-

nea and expectorating gray sputum. Some distention was present. Her temperature was 102.2 F. Codeine was given for relief of pain. November 3 the chest was examined roentgenologically, and the condition of the patient was reported to the anesthesia department. She was found dyspneic and anxious and cyanotic and she was coughing and retching almost continuously. The temperature was 102.2 F. and the pulse rate 120. Roentgen ray examination showed diffuse clouding of the entire left lung, and the central shadows were displaced toward this side, with increased aeration on the right. Cocainization of the larynx was done, with expectoration in a few minutes of a large mucus plug and large amounts of purulent mucus. A roentgenogram taken at once showed partial clearing of the left pulmonary field with progressive clearing November 4 and 5. Inhalations of carbon dioxide and oxygen were started and also chemotherapy with sulfathiazole; blowing up of blow bottles was instituted, with relief of the collapse, though a pulmonic process in the base of the left lung persisted until November 17.

This case illustrates the necessity for recognition and treatment of a condition of collapse at once before pneumonia begins, which happens speedily in a congested and airless area of lung and which prolongs the recovery period a number of days.

Case 2.—E. D., a poorly nourished white man 48 years old, was brought to surgery on July 15 for repair of a recurrent inguinal hernia on the left side, which had been repaired eight years ago. His history was noncontributory except for the fact that he smoked excessively and had a chronic nonproductive cough. Physical examination revealed carious teeth with spongy, receding gums and a moderately injected pharynx. A few moist rales were heard in the left axilla. Twelve milligrams of pontocaine hydrochloride solution was given in the second lumbar space; the hernia was repaired without incident in fifty-five minutes, and the patient was returned to the ward in good condition. Inhalations of carbon dioxide and oxygen were refused, and the patient refused to take deep breaths or to cough. A roentgenogram was taken July 16 on account of pleuritic pain in the right base of the chest, with a friction rub; it revealed clouding of the base of the right lung with elevation of the diaphragm, and was interpreted by the roentgen ray department as "suggestive of pleurisy." The temperature at this time was 99.8 F. Morphine sulfate, ⅙ grain [0.01 Gm.], was being given three times a day. His temperature rose to 102.6 F. on July 17, and he had severe pain in the back. Administration of sulfathiazole was begun, with rapid improvement. The temperature was 99 F. On July 19 another roentgenogram was taken on account of increased pain, which revealed a large shadow above the right side of the diaphragm with a shift of the trachea to the right. The throat was cocainized with 10 per cent cocaine solution, and the patient coughed up a large mucus plug and stated that the pain was less intense. He remained comfortable, and his condition steadily improved. Use of sulfathiazole together with ammonium sulfate was continued for forty-eight hours with no further incident.

Case 3.—N. G., a poorly nourished woman 27 years old, was brought to surgery on June 19 for suspension and perineorrhaphy. The history revealed chronic pelvic inflammatory disease, with recent septic abortion with hemorrhage. The hemoglobin content was 81 per cent, the sugar content 104 mg., the nonprotein nitrogen level 27.9 mg. and the creatinine content 1.4 mg. per hundred cubic centimeters. The operation preceding this one had been canceled, and so the patient was brought to the operating room and premedication of seconal, 3 grains (0.19 Gm.), given at 7:30 a. m., morphine sulfate 1/6 grain (0.01 Gm.), and scopolamine hydrobromide 1/200 grain (0.0003 Gm.), being given at the same time. Administration of cyclopropane was begun at 7:42 a. m., followed by closed ether. The surgeon had insisted that the anesthetic be begun immediately, stating that it made no difference when the premedication was given. A dilation and curettage, perineorrhaphy, trachelorraphy and Gilliam's suspension were done during the next hour and thirty minutes, and the patient was returned to the ward in good condition at 9:50 a. m. At 10:30 a. m. on June 20 she was seized with sudden pain in the right side of the chest, with dyspnea, anxiety and tachycardia. Examination revealed the right side of the chest unexpansive on respiration, an absence of breath sounds in the right base and coarse rales heard in the right apex. Roentgen ray examination showed massive collapse of the right lung, with the mediastinum and trachea shifted to the right. Cocainization of the throat was done within half an hour and coughing encouraged. A large hard mucus plug was expectorated, with the patient experiencing great relief of dyspnea and anxiety. The cyanosis improved almost at once. Roentgen ray examination showed partial clearing of the chest. Inhalations of carbon dioxide and oxygen and blowing up of blow bottles were started. By 4 p. m. the roentgenogram revealed the right side of the chest nearly clear, with the diaphragm returned to a normal level. Sulfathiazole was discontinued June 21, and the patient remained free from further symptoms.

Case 4.—R. O., a poorly nourished woman 43 years old, was brought to surgery March 18 for exploratory laparotomy on account of large pelvic masses. She had been bleeding profusely for four months, with a hemoglobin content on her admission to the hospital (February 26) of 27 per cent. The rest of the history was noncontributory, and physical examination at this time revealed exceedingly carious teeth and spongy gums and a soft blowing mitral systolic murmur disappearing on exercise. Hemoglobin content at the time of operation was 65 per cent, the sugar content 108 mg., the nonprotein nitrogen level 31.6 mg. and the creatinine level 1.7 mg. per hundred cubic centimeters. The urine test revealed nothing abnormal. Premedication of morphine, 1/6 grain (0.01 Gm.), and scopolamine hydrobromide, 1/200 grain (0.0003 Gm.), was given and fifty-five minutes later drop ether was begun, as the surgeon insisted that ether be used for all of his patients. Bilateral salpingo-oophorectomy was done during a one hour operation without incident, and the patient was returned to the ward in good condition at 10:30 a. m. Her condition remained good until March 19 at 8 p. m., when she complained of shortness of breath and pain in the right side of the chest. The temperature was 102.8 F. and the pulse rate 160. There was an absence of breath sounds in the right side and hyperresonance in the left side of the chest. The medical service was consulted and gave advice to treat the patient as for pneumonia. Administration of sulfapyridine was started, but by morning the patient was worse and symptoms were more pronounced. A roentgenogram taken during the morning revealed a complete collapse of the right side of the chest (fig. 1 *A*). At 2:15 p. m. the anesthesia department was consulted, and the throat was cocainized at once with 10 per cent cocaine. During the procedure the patient was thrown into a paroxysm of coughing that resulted in the expectoration of copious quantities

of mucopurulent material; breathing immediately became easier, and breath sounds began to be heard over the right side of the chest. Check roentgenograms one and one-half hours later revealed reexpansion of the right lung, with change of the heart shadow to a more nearly normal position (fig. 1 *B*). Inhalations of carbon dioxide and oxygen every half hour were begun, blow bottles were blown up every hour and administration of sulfapyridine was continued. Roentgenograms on March 21 revealed an almost complete reexpansion of the lung, with return of the tracheal shadow to the normal medial position (fig. 1 *C*). Three days later roentgenograms showed complete clearing of the lung, with return of a normal temperature (fig. 1 *D*).

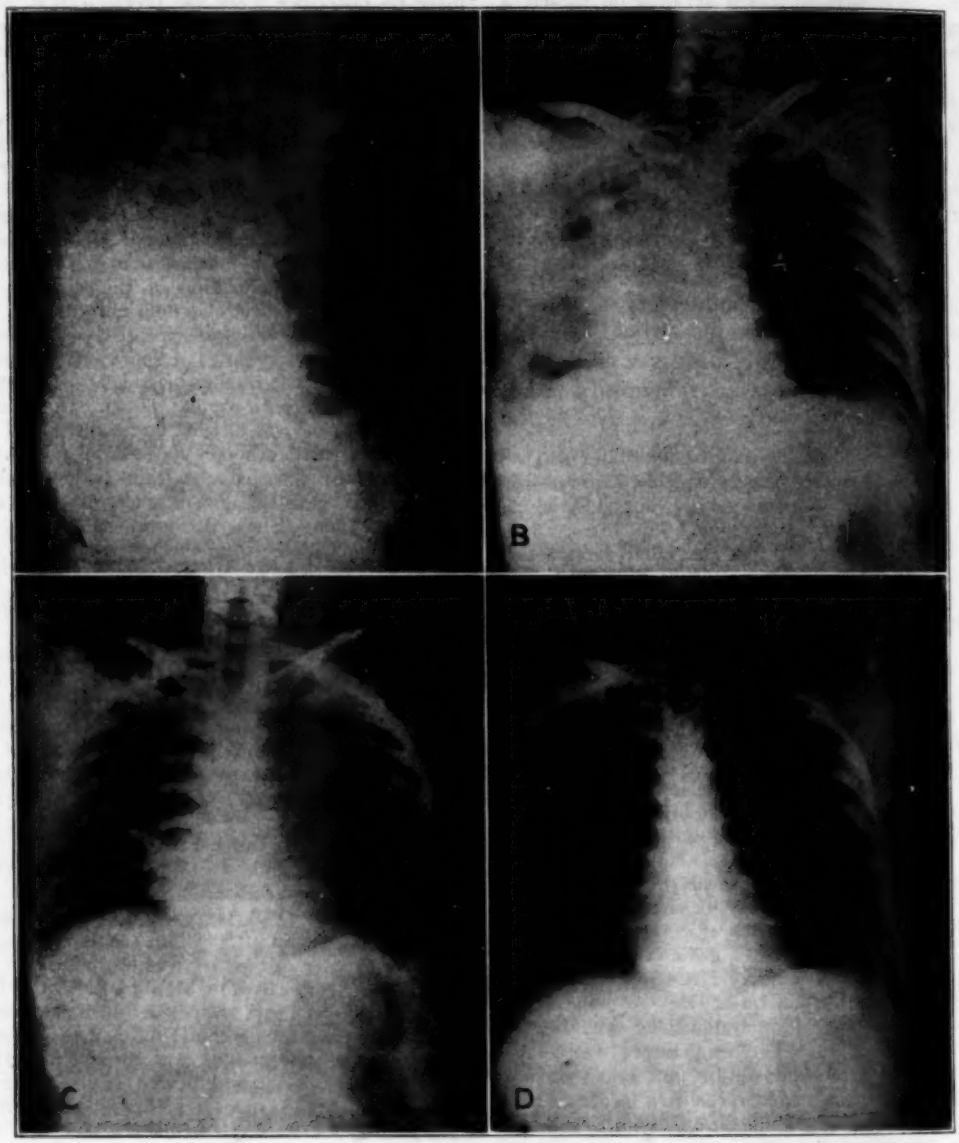

Fig. 1 (case 4).—*A*, immediately before treatment showing complete collapse of the right lung, with shifting of the tracheal shadow and the heart shadow to the right. *B*, one and one-half hours after cocainization of throat and expectoration of large quantities of mucus, showing partial reexpansion of right lung. *C*, on morning following cocainization of throat, showing almost complete reexpansion of right lung and shifting of tracheal shadow to normal position. *D*, three days after treatment for collapse, showing complete restoration and clearing of lung.

Case 5.—N. S., a well nourished woman 43 years old, was brought to surgery January 22 for exploratory laparotomy for abdominal pain and hyperesthesia of the abdominal wall. Bilateral salpingectomy, oophorectomy on the left side and supravaginal hysterectomy had been done nine months previously. Severe pain at the upper end of the incision intermittently since this operation was the chief complaint. The other history was noncontributory. Physical examination revealed no abnormalities other than extremely carious teeth. Pentobarbital sodium, 1½ grains (0.09 Gm.), was given at 8 a. m., and morphine sulfate, ⅛ grain (0.007 Gm.), and scopolamine, 1/200 grain (0.0003 Gm.), were given at 10:10. Nitrous oxide, 92.8 per cent, was begun

at 10:30 a. m., followed by closed ether anesthesia for maintenance. Lysis of extensive adhesions of the omentum into the pelvis was done. The operation lasted an hour and fifty-three minutes, and the patient was returned to the ward in good condition at 12:50 p. m.

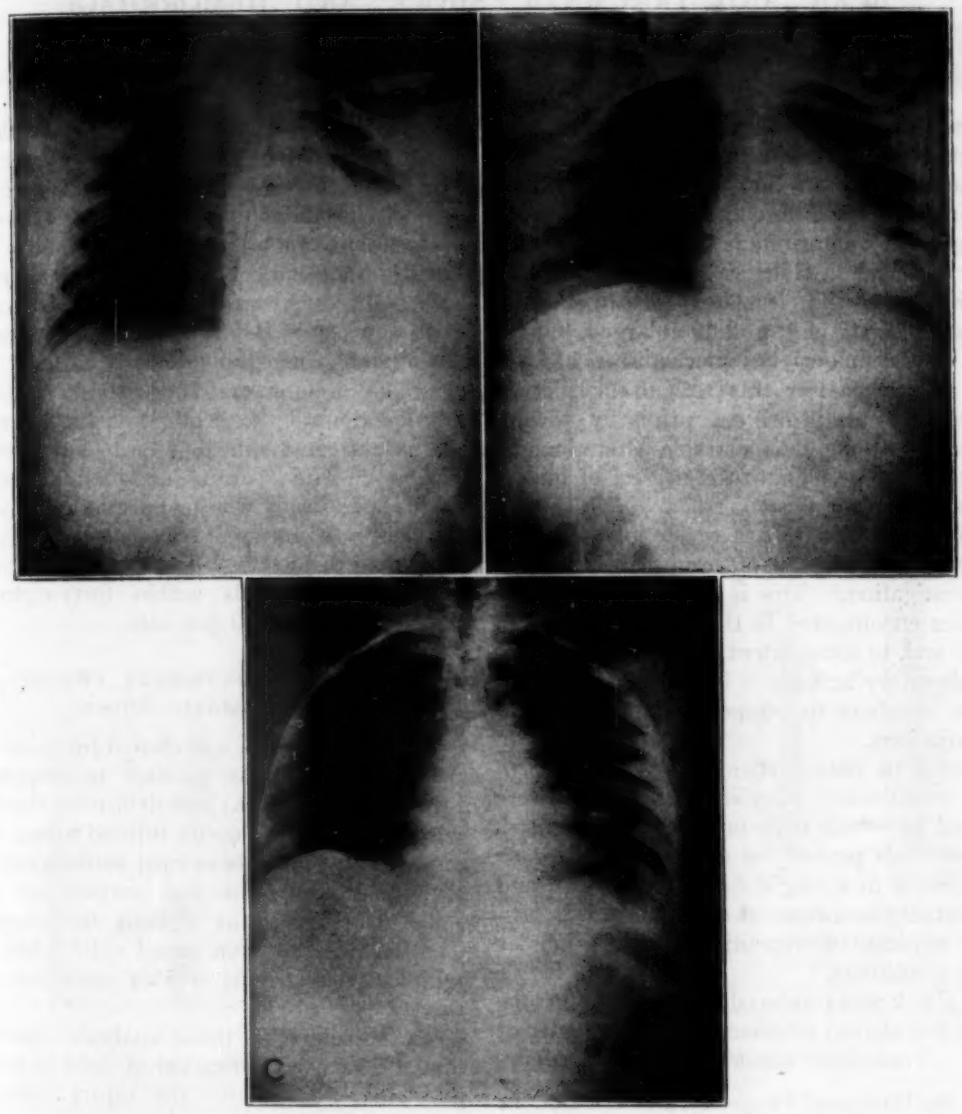

Fig. 2 (case 5).—*A*, showing collapse of the lower lobe of the left lung before treatment. *B*, showing reexpansion of the left base shortly after treatment and two hours after initial collapse. *C*, showing complete reexpansion and clearing of the left lung ten hours after initial collapse, with immediate treatment.

She was talking at 1:50 p. m. At 6 a. m. January 23, she was found cyanotic and complaining of pain in the chest. A roentgenogram revealed collapse of the left lung (fig. 2*A*). Swabbing of the throat with epinephrine and cocaine was started, with inhalations of carbon dioxide and oxygen and use of ammonium sulfate and sulfapyridine. Copious expectoration resulted from cocainization of the throat, with pronounced relief experienced by the patient. A roentgen ray examination at 8 a. m. revealed two-thirds clearing of the left base, with still a slight shift of the mediastinal shadow (fig. 2*B*). Roentgen ray examination at 4 p. m. showed complete clearing of the base of the left lung (fig. 2*C*).

This case also illustrates the value of immediate treatment in preventing pneumonia following collapse of the lung.

ELECTROLYTE CHANGES AND CHEMOTHERAPY IN EXPERIMENTAL BURN AND TRAUMATIC SHOCK AND HEMORRHAGE

SANFORD M. ROSENTHAL, M.D., AND HERBERT TABOR, M.D.
BETHESDA, MD.

During the past few years, observations have been made on experimentally produced burn and traumatic shock and death from hemorrhage in over 10,000 small laboratory animals. This report of our results is being made because of their possible significance in clinical practice.

Knowledge of the circulatory disturbances in shock has recently been greatly enlarged, but the nature of the underlying mechanisms has remained obscure. For this reason the therapy of shock has been directed primarily toward correction of these demonstrable alterations in the circulation, perhaps to the neglect of important changes in the tissues.

In the field of therapy, a review of the literature reveals a diversity of results from laboratory investigation.[1] This is an expression of the difficulties encountered in the standardization of methods and, to some extent, of the fact that with large laboratory animals it is difficult to employ adequate numbers to compensate for wide biologic variations.

In order to obtain standardized and reproducible conditions, simplified methods were developed by which mice or rats could be used. These methods permit the use of a hundred or more animals in a single day's experiment, and with mortality as a basis of comparison it is possible to evaluate therapeutic procedures under uniform conditions.

Burn shock was produced by immersion to the axilla of the shaved etherized animal in water at 70 C.[2] Traumatic shock was produced by placing tourniquets (rubber bands) on the hind-legs of etherized animals for two or more hours.[3] Anesthesia was employed only during the brief period of application of the trauma. Hemorrhage was carried out by placing the cut tails in measuring cylinders containing warm oxalate solution. Bleeding was produced in two stages, with a one hour intermission between bleedings; the first bleeding amounted to 2.25 per cent of the body weight, and the second bleeding was continued until the death of a high percentage of the untreated animals (4.5 to 5 per cent body weight). The quantity of blood loss required to produce death was taken as a basis of comparison.[4] All forms of trauma were so standardized that the average mortality among control (untreated) animals within forty-eight hours was greater than 90 per cent.

FLUID AND ELECTROLYTE CHANGES IN TRAUMATIC SHOCK

Tourniquet shock was chosen for these experiments because it is possible to amputate the injured tissues (legs) and determine the changes which occur in the entire injured area. Control analyses on groups of normal animals kept under the same conditions and carried out at the same time served as a basis for comparison. This technic has been found valid when pooled samples from groups of 5 or more animals are used.

The results[5] of these analyses demonstrate that the local accumulation of fluid in untreated mice two hours after the injury amounts to

From the Division of Physiology, National Institute of Health, United States Public Health Service.

1. Adequate references to the large literature are not possible in this paper. The following reviews may be consulted: Harkins, H. N.: Recent Advances in the Study and Management of Traumatic Shock, Surgery **9**:231 (Feb.); 447 (March); 607 (April) 1941. Blalock, A.: Principles of Surgical Care, Shock and Other Problems, St. Louis, C. V. Mosby Company, 1940. Moon, V. N.: Shock: Its Dynamics, Occurrence, and Management, Philadelphia, Lea & Febiger, 1942. More recent references may be found in the papers cited below.

2. Rosenthal, S. M.: Experimental Chemotherapy of Burns and Shock: (*a*) I. Methods; II. Effects of Local Therapy upon Mortality from Shock, Pub. Health Rep. **57**:1923-1935 (Dec. 18) 1942; (*b*) III. Effects of Systemic Therapy on Early Mortality, ibid. **58**:513-522 (March 26) 1943.

3. Rosenthal, S. M.: Experimental Chemotherapy of Burns and Shock: IV. Production of Traumatic Shock in Mice; V. Therapy with Mouse Serum and Sodium Salts, Pub. Health Rep. **58**:1429-1438 (Sept. 24) 1943.

4. Tabor, H.; Kabat, H., and Rosenthal, S. M.: The Chemotherapy of Burns and Shock: VI. Standardized Hemorrhage in the Mouse; VII. Therapy of Experimental Hemorrhage, Pub. Health Rep. **59**:637-638 (May 19) 1944.

5. Tabor, H., and Rosenthal, S. M.: Experimental Chemotherapy of Burns and Shock: VIII. Effects of Potassium Administration, of Sodium Loss, and Fluid Loss in Tourniquet Shock, Pub. Health Rep. **60**:373-380 (April 6) 1945; Electrolyte Changes in Tourniquet Shock, ibid. **60**:401-419 (April 13) 1945.

3 per cent of body weight, a value in agreement with that originally found by Blalock, Harkins and others [2] (chart 1).

Along with the local accumulation of fluid, sodium enters the injured area; this amounts to 0.10 milliequivalent for a 15 Gm. mouse and is greater by 0.03 milliequivalent than the amount which can be accounted for by the local increase in fluid. This local increase in sodium is equivalent to the entire sodium in the circulating blood or one fourth of that in the total extracellular fluid. This rapid accumulation of fluid and sodium occurs at the expense of the uninjured tissues, which are correspondingly dehydrated.

During the same two hour period, the injured area loses approximately one third of its total potassium, amounting to 0.03 milliequivalent per 15 Gm. mouse (chart 1). This quantity of potassium is thus released from the traumatized area into the rest of the body; its significance will be discussed later. It is of interest that the potassium loss from the injured area corresponds approximately to the sodium gain, which is in excess of that calculated to enter with the edema fluid, suggesting that an exchange of potassium

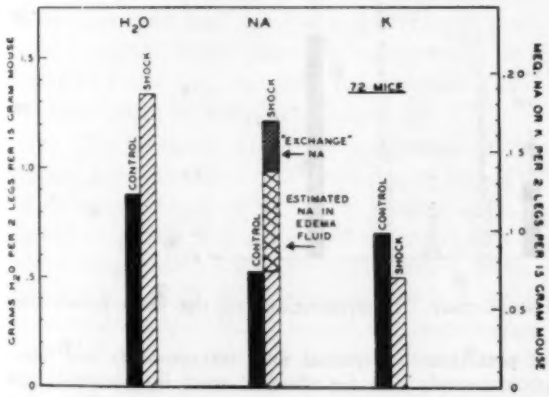

Chart 1.—Changes in water, sodium and potassium in the hindlegs of mice subjected to tourniquets for two hours. Analyses two hours after removal of tourniquets. Values represent the total amounts in the two legs of a 15 Gm. mouse. Control values from normal mice studied simultaneously.

for sodium takes place in injured tissues; evidence that this can occur in vitro has been presented by Eichelberger and Hastings [6] and that it can occur in vivo by Manery and Solandt.[7]

6. Hastings, A. B., and Eichelberger, L.: The Exchange of Salt and Water Between Muscle and Blood: I. The Effect of an Increase in Total Body Water Produced by the Intravenous Injection of Isotonic Salt Solutions, J. Biol. Chem. **117**:73-93 (Jan.) 1937.

7. Manery, J., and Solandt, D.: Studies in Experimental Traumatic Shock with Particular Reference to Plasma Potassium Changes, Am. J. Physiol. **138**:499-511 (Feb.) 1943.

The magnitude of these local changes in fluid and electrolyte have also been studied by Fox and Keston [8] with the use of radioactive sodium, and our results are substantially in agreement.

URINARY STUDIES

In addition to local alterations in the injured area, some estimate of the electrolyte changes

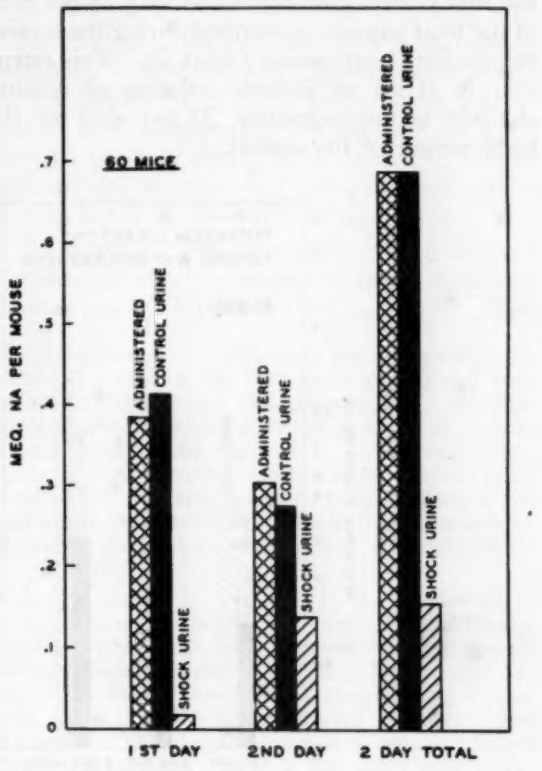

Chart 2.—Sodium excretion in urine of normal and shocked (tourniquet) mice. Both groups received 0.385 milliequivalent of sodium orally the first day and 0.302 milliequivalent the second day. Practically complete retention the first day and 72 per cent retained in forty-eight hours. Nine-tenths per cent solution of sodium chloride was administered.

that are occurring in the rest of the body and of fluid and electrolyte needs in shock may be obtained by urinary studies. Mice in which death from shock was prevented by therapy with 0.9 per cent solution of sodium chloride were placed in metabolism cages for quantitative collection of urine. Normal animals similarly treated with sodium chloride served as a basis for comparison.

The quantity of sodium retained by the shocked animal after administration of isotonic solution of sodium chloride may serve as some index of

8. Fox, C. L., Jr., and Keston, A. S.: The Mechanism of Shock from Burns and Trauma Traced with Radiosodium, Surg., Gynec. & Obst. **80**:561-567 (June) 1945.

the sodium requirement during the shock period. The local accumulation of fluid in the injured area is only a partial indication of this deficit; this was shown by Fox [9] in burned patients and in shocked mice. We have similarly found in tourniquet-shocked mice that when 0.38 milliequivalent of sodium per mouse is administered on the first day and 0.3 milliequivalent on the second day there is complete retention during the first twenty-four hours and only 28 per cent of the total amount is excreted during the second twenty-four hour period (chart 2). This retention in terms of isotonic solution of sodium chloride is approximately 20 per cent of the body weight of the animal.

SIGNIFICANCE OF CHANGES

What importance can be attributed to these fluid and electrolyte disturbances, and what is their significance in terms of therapy?

First, they indicate a dehydration of the sodium-containing extracellular fluid compartment.[10] Since the blood constitutes only one fourth of this reservoir and since the sodium and fluid loss is as great as or greater than the total amounts contained in the plasma, the major deficit must occur in the tissues. It is not to be expected that a normal plasma volume can be maintained with any permanency until the tissue dehydration is also corrected. This conclusion is also corroborated by the therapeutic studies reported later, which reveal that optimum survival from a fatal degree of trauma is not achieved until 10 to 15 per cent of the body weight of isotonic solution of sodium salts is administered.

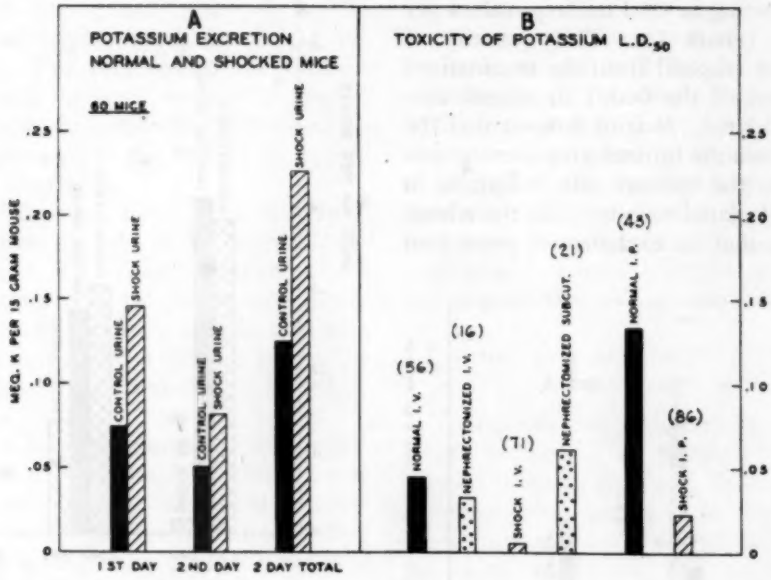

Chart 3.—*A*, potassium excretion in normal and in shocked mice. Determinations on the same urines used for sodium analyses (chart 2).

B, the L.D.$_{50}$ (lethal dose for 50 per cent of animals) of potassium for normal mice intravenously and intraperitoneally, for nephrectomized mice intravenously and subcutaneously and for shocked mice intravenously and intraperitoneally. The toxicity for shocked animals is increased six to nine times over normal. Figures in parentheses indicate number of animals used.

That this retention of sodium is not due to anuria is indicated by the fact that during this period potassium is excreted in excess. Increases above the control values amounting to 0.075 milliequivalent per mouse on the first day and 0.025 milliequivalent on the second day were obtained (chart 3). This has been shown to be more than twice the amount of potassium that is liberated from the injured area in treated mice, indicating that potassium is also released from nontraumatized areas in shock.[5]

Second, the quantity of potassium released in the body suggests that a reevaluation be made of its significance as a toxic factor in shock. On

9. Fox, C. L., Jr.: Oral Sodium Lactate in the Treatment of Burn Shock, J. A. M. A. **124**:207-212 (Jan. 22) 1944. Fox and Keston.[8]

10. (*a*) Gamble, J. L.: Chemical Anatomy, Physiology, and Pathology of Extracellular Fluid, Boston, Harvard Medical School, 1942. (*b*) Hastings, A. B.: The Electrolytes of Tissues and Body Fluids, in Harvey Lectures, 1940-1941, Baltimore, Williams & Wilkins Company, 1941, vol. 36, p. 91. (*c*) Peters, J. P.: Water Exchange, Physiol. Rev. **24**:491-531 (Oct.) 1944.

a basis of various experimental evidence, potassium has been suggested in this role.[11] While some recent evidence supports this view,[12] the importance of potassium has not been generally accepted. This is due in part to the fact that previous studies have been confined to changes in the blood or isolated tissues, and consequently quantitative data on the magnitude of the total changes were not available and also because the observed alterations were interpreted in terms of the normal rather than the shocked animal.

The following observations have been made[5] in an attempt to evaluate the significance of the potassium release in traumatic shock:

(*a*) In a shocked animal the toxicity of administered potassium increases six to nine times above that for a normal animal (chart 3). This is not the result of a general increase in susceptibility to toxic agents, for under similar conditions the toxicity of magnesium and quinidine (used as drug controls) was less than doubled.

(*b*) The amount of potassium released in shock, as indicated by analyses of the entire injured area and by urinary studies, is toxic for a normal animal when given intravenously or intraperitoneally and for an anuric (nephrectomized) animal when given subcutaneously and is several times the fatal dose for a shocked animal when given by any route (chart 3).

(*c*) The elevation of serum potassium in the shocked animal cannot be interpreted in terms of the elevation required to kill a normal animal. Rabbits in shock that are killed by injections of potassium chloride show terminal serum potassium levels (13.20 milliequivalent per liter, with a standard error of 0.22) within the same range as those found in shocked rabbits without treatment with potassium chloride that die from shock several hours later (12.08 milliequivalent with a standard error of 0.35). These values are lower than those obtained for normal rabbits that are killed by injections of potassium chloride (16.58 milliequivalent with a standard error of 0.68). These results suggest that the moderate elevations of serum potassium seen in shock may have greater significance than is usually attributed to them, particularly in relation to the terminal phases of this condition.

Not only is the shocked animal abnormally sensitive to administered potassium. It is possible to produce withdrawal of fluid and sodium from the body by the intraperitoneal injection of dextrose solutions.[13] By the use of this technic, it has been demonstrated that the shocked animal is also highly susceptible to any additional loss of fluid or sodium.[5]

The evidence indicates that these three factors, fluid loss, sodium loss and potassium toxicity, are interdependent. While in shock the magnitude of each change may not in itself be sufficient to produce death, their combined effects augment one another and may have an important influence on mortality in shock.

There are various types and various degrees of shock, in which a variety of other biochemical changes have been shown to exist[14]; like-

11. Scudder, J.: Shock: Blood Studies as a Guide to Therapy, Philadelphia, J. B. Lippincott Company, 1940.

12. Bywaters, E. G. L., and Popjak, G.: Experimental Crushing Injury, Surg., Gynec. & Obst. **75**:612-627 (Nov.) 1942. Bywaters, E. G. L.: Ischemic Muscle Necrosis, J. A. M. A. **124**:1103-1109 (April 15) 1944. Clarke, A. P. W., and Cleghorn, R. A.: Chemical Studies of Tissue Changes in Adrenal Insufficiency and Traumatic Shock, Endocrinology **31**:597-606 (Dec.) 1942.

13. Schechter, A. J.: Electrolyte and Volume Changes in Fluids Injected into the Peritoneal Cavity, Yale J. Biol. & Med. **4**:167-185 (Dec.) 1931. Darrow, D. C., and Yannet, H.: Changes in Distribution of Body Water Accompanying Increase and Decrease in Extracellular Electrolyte, J. Clin. Investigation **14**:266-275 (March) 1935; Metabolic Studies of Changes in Body Electrolyte and Distribution of Body Water Induced Experimentally by Deficit of Extracellular Electrolyte, ibid. **15**:419-427 (July) 1936.

14. (*a*) Russell, J. A.; Long, C. N. H., and Engel, F. L.: Biochemical Studies on Shock: Role of Peripheral Tissues in Metabolism of Protein and Carbohydrate During Hemorrhagic Shock in Rat, J. Exper. Med. **79**: 1-7 (Jan.) 1944. Engel, F. L.; Harrison, H. C., and Long, C. N. H.: Biochemical Studies on Shock: Role of Liver and Hepatic Circulation in Metabolic Changes During Hemorrhagic Shock in Rat and Cat, ibid. **79**: 9-22 (Jan.) 1944. Russell, J. A.; Long, C. N. H., and Wilhelmi, A. E.: Biochemical Studies on Shock: Oxygen Consumption of Liver and Kidney Tissue from Rats in Hemorrhagic Shock, ibid. **79**:23-33 (Jan.) 1944. (*b*) Shen, S. C., and Ham, T. H.: Studies on Destruction of Red Blood Cells, New England J. Med. **229**:701-713 (Nov. 4) 1943. (*c*) Govier, W. M.: Studies on Shock Induced by Hemorrhage: III. The Correlation of Plasma Thiamin Content with Resistance to Shock in Dogs, J. Pharmacol. & Exper. Therap. **77**:40-49 (Jan.) 1943. (*d*) Aub, J. C.; Brues, A. M.; Dubos, R.; Kety, S. S.; Nathanson, I. T.; Pope, A., and Zamecnic, P. D.: Bacteria and the Toxic Factor in Shock, War Med. **5**:71-73 (Feb.) 1944. (*e*) Prinzmetal, M.; Freed, S. C., and Kruger, H. E.: Pathogenesis and Treatment of Shock Resulting from Crushing of Muscle, ibid. **5**: 74-79 (Feb.) 1944. (*f*) Glenn, W. L.; Muus, J., and Drinker, C. K.: Observations on the Physiology and Biochemistry of Quantitative Burns, J. Clin. Investigation **22**:451-459 (May) 1943. Perlmann, G. E.; Glenn, W. W., and Kaufman, D.: Changes in Electrolytic Pattern in Lymph and Serum in Experimental Burns, ibid. **22**:627-633 (July) 1943. (*g*) Ricca, R. A.; Fink, K.; Katzin, L. I., and Warren, S. L.: Effect of Environmental Temperature on Experimental Traumatic Shock in Dogs, J. Clin. Investigation **24**:127-139

(Footnote continued on next page)

wise, unknown factors remain to be discovered. The aforementioned concept does not preclude the possibility that such factors may also play a primary or secondary role in death from shock.

THERAPEUTIC STUDIES

It should be made clear that the observations on therapy are concerned with the first forty-eight hours following experimental trauma. While delayed deaths rarely occurred after tourniquet shock or hemorrhage, following burns a progressive loss of weight with death within three weeks was frequently seen. This condition was observed regardless of the type of early therapy and is not to be confused with the mortality during the shock phase.

It should also be pointed out that we have been unable to produce delayed hemorrhagic shock in mice or rats with sufficient constancy to employ such a technic for evaluation of therapy. The following results are accordingly based on acute death from loss of blood, as outlined at the beginning of this paper.

Even when every effort has been made to obtain uniformity of conditions, variations in therapeutic response may occur from one day to another, particularly if the environmental temperature is not controlled. The dominant influence of temperature on therapeutic response is discussed in the following paragraphs.

It is believed that for accurate evaluation of experimental therapy two conditions must be met: simultaneous comparisons and an adequate number of comparisons. Even under our laboratory conditions, with standardized trauma, with relative uniformity of animals as to size, sex and diet, with constant environmental temperature and with simultaneous comparisons, at least 30 to 40 animals in each group are necessary for results within 20 per cent accuracy. Conclusions based on 15 animals may be subject to an error as high as 50 per cent.

If this variability is observed under controlled conditions in the laboratory, it is important for the clinician to realize the fallacy of basing conclusions on mortality data from small groups of cases, in which no approach to uniformity can possibly be attained.

The results which we have obtained in the three types of experimental injury have shown a similarity in response to fluid and electrolyte therapy that indicates an underlying disturbance common to all of them. After a fatal degree of burn, trauma or hemorrhage, the majority of animals will survive if 10 to 15 per cent of their body weight of an isotonic solution of a sodium salt is administered by any route (charts 4 and 5).

With the exception of the earlier observations of Davidson [15] and Underhill [16] and the more recent studies of Allen,[17] these results could not be anticipated from the previous work in this field.[1] However, experiments in agrement with these observations have been recently made by Fox [8] and Prinzmetal [18] on mice, by Katz, Friedberg and Asher,[19] Swingle and Kleinberg,[20] Warren, Merrill and Stead,[21] Scott, Worth and Robbins [22] and Moyer and colleagues [23] on dogs and by Locke [24] and Harkins [25] on rats.

(March) 1945. Ricca, R. A.; Fink, K.; Steadman, L. T., and Warren, S. L.: Distribution of Body Fluids of Dogs in Traumatic Shock, ibid. **24**:140-145 (March) 1945. Ricca, R. A.; Fink, K., and Warren, S. L.: Effect of Sulfadiazine, Antitoxins, Globulins and Dog Plasma on Dogs in Traumatic Shock Under Sodium Pentobarbital Anesthesia, ibid. **24**:146-148 (March) 1945. Katzin, L. I.; Ricca, R. A., and Warren, S. L.: Effect of Environmental Temperature and Anesthesia on Survival of Tourniquet Shock in Rabbits, ibid. **24**:149-151 (March) 1945. Katzin, L. I., and Warren, S. L.: Thiamine-Deficient Diet in Tourniquet Shock in Rats, ibid. **24**:152-153 (March) 1945. Scholz, D. E., and others: Study of Body Temperature and Water Content in Shock Produced by Continuous Intravenous Injection of Adrenalin, With and Without Anesthesia, ibid. **24**:154-159 (March) 1945. Footnote 12.

15. Davidson, E. C.: Sodium Chloride Metabolism in Cutaneous Burns and Its Possible Significance for a Rational Therapy, Arch. Surg. **13**:262-277 (Aug.) 1926.

16. Underhill, F. P.: The Significance of Anhydremia in Extensive Superficial Burns, J. A. M. A. **95**:852-857 (Sept. 20) 1930.

17. Allen, F. M.: Physical and Toxic Factors in Shock, Arch. Surg. **38**:155-180 (Jan.) 1939; Theory and Therapy of Shock: Varied Fluid Injections, Am. J. Surg. **62**:80-104 (Oct.) 1943.

18. Prinzmetal, M.; Hechter, O.; Margoles, C., and Feigen, G.: A Principle from Liver Effective Against Shock Due to Burns, J. Clin. Investigation **33**:795-806 (Sept.) 1944. Hechter, O.; Bergman, H. C., and Prinzmetal, M.: Comparison of Therapeutic Effectiveness of Serum and Sodium Chloride in Scald Shock, Am. Heart J. **29**:484-492 (April) 1945.

19. Katz, L. N.; Friedberg, L., and Asher, R.: Efficacy of Isotonic Sodium Chloride and Glucose in Preventing Shock Following Venous Occlusion of a Limb in the Dog, Am. J. Physiol. **140**:65-71 (Oct.) 1943.

20. Swingle, W. W., and Kleinberg, W.: Plasma, Gelatin and Saline Therapy in Experimental Wound Shock, Am. J. Physiol. **141**:713-721 (July) 1944.

21. Warren, J. V.; Merrill, A. J., and Stead, E. A., Jr.: The Role of the Extracellular Fluid in the Maintenance of a Normal Plasma Volume, J. Clin. Investigation **22**:635-641 (Sept.) 1943.

22. Scott, C. C.; Worth, H. W., and Robbins, E. B.: Comparative Value of Some Blood Substitutes Used for Treatment of Experimental Shock, Arch. Surg. **48**:315-318 (April) 1944.

23. Moyer, C. A.; Coller, F. A.; Iob, V.; Vaughn, H. H., and Marty, D. A.: Study of the Interrelation-

Therapy in most experiments on burns and tourniquet shock was begun one-half to one hour after the injury, when visible symptoms of shock, namely prostration and dyspnea, were present. Deaths in untreated animals had already occurred at the time therapy was begun. Even when therapy was delayed beyond this point, favorable responses to administration of saline solution have been obtained. In hemorrhage experiments 10.5 per cent of the mice had died at the time of onset of therapy, which was administered in the interval between bleedings (after a blood loss of 2.25 per cent body weight).

The percentage of survivors is considerably lower if only 5 per cent of body weight of an isotonic solution of a sodium salt is given (chart 4); this, in part, explains the lack of success with saline therapy frequently reported from the laboratory and clinic, where this amount has usually represented the maximum therapeutic dose.

A comparison of various salts has shown that the beneficial effect is a function of the sodium ion. A similar response was obtained with all the sodium salts we have tested, while other cations—potassium, calcium, magnesium, cesium, rubidium and lithium—were either deleterious or without effect.[26]

Likewise, isotonic dextrose solutions had little effect (chart 5); given intraperitoneally (and this probably applies to other methods of administration such as hypodermoclysis), they were decidedly harmful [5] because they temporarily withdrew water and sodium from the body. Hypertonic solutions in general were found to be less effective than isotonic solutions, perhaps for the same reason.

Water administered orally, 8 to 10 per cent body weight, was ineffective in burn shock (91 per cent mortality in 50 mice as compared with 95 per cent in 50 controls). In tourniquet shock some benefit from this was seen (50 per cent mortality in 48 mice as compared with 90 per cent in 48 controls). In hemorrhage only slight benefit from water was obtained,[4] and this was shown to be due to blood dilution; in terms of hemoglobin loss, the animals treated with water were able to withstand no greater depletion than the controls.

Fruit juices, because of their high potassium content, are definitely harmful in experimental shock. An experiment in tourniquet shock demonstrated that 5 per cent body weight of

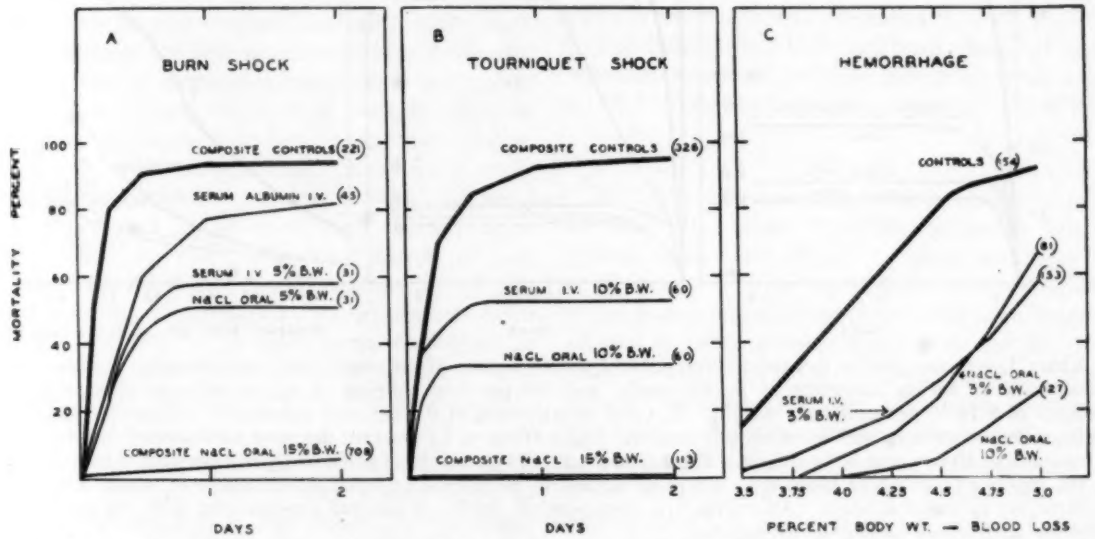

Chart 4.—The similar therapeutic response of mouse serum administered intravenously and saline solution administered orally in burn and tourniquet shock and hemorrhage, given in equivalent doses on a basis of body weight (B.W.). Concentrated human serum albumin (25 per cent) is less effective than serum in doses with equivalent protein content but less sodium chloride. Also the increased effectiveness of larger doses of isotonic solution of sodium chloride (10 to 15 per cent body weight) is indicated. Each curve is a composite of results of several experiments. Figures in parentheses indicate number of mice represented.

ship of Salt Solutions, Serum and Defibrinated Blood in the Treatment of Severely Scalded, Anesthetized Dogs, Ann. Surg. **120**:367-376 (Sept.) 1944.

24. Locke, W.: An Experimental Method for Evaluating Blood Substitutes, Science **99**:475-476 (June 9) 1944.

25. Harkins, H. N.: Personal communication to the authors.

26. Rosenthal.[2a] Tabor and Rosenthal.[5]

orange juice by mouth was rapidly lethal (chart 5 *B*).

These results with various electrolytes and fluids, along with the demonstrated sodium deficiency, clearly indicate that in the therapy of shock, fluids other than isotonic solutions of sodium salts may have little value or may even be harmful.

Sodium lactate was employed by Fox [9] in the first clinical appraisal of therapy with oral administration of large amounts of isotonic solutions of sodium salts, and he has reported promising results. Isotonic solutions of this salt (1.75 per cent) are palatable by mouth and withstand boiling for parenteral injection. The lactate ion serves to correct the acidosis that is present in varying degrees in shock. With the amounts required, however, the possibility of producing alkalosis exists. While Fox has found that this hazard is not important when careful observation under hospital conditions can be enforced, for general use a mixture of 1 part of 1.75 per cent solution sodium lactate with 2 parts of 0.9 per cent solution of sodium chloride would seem preferable. This mixture has been recommended by the Shock Committee of the National Research Council.[27]

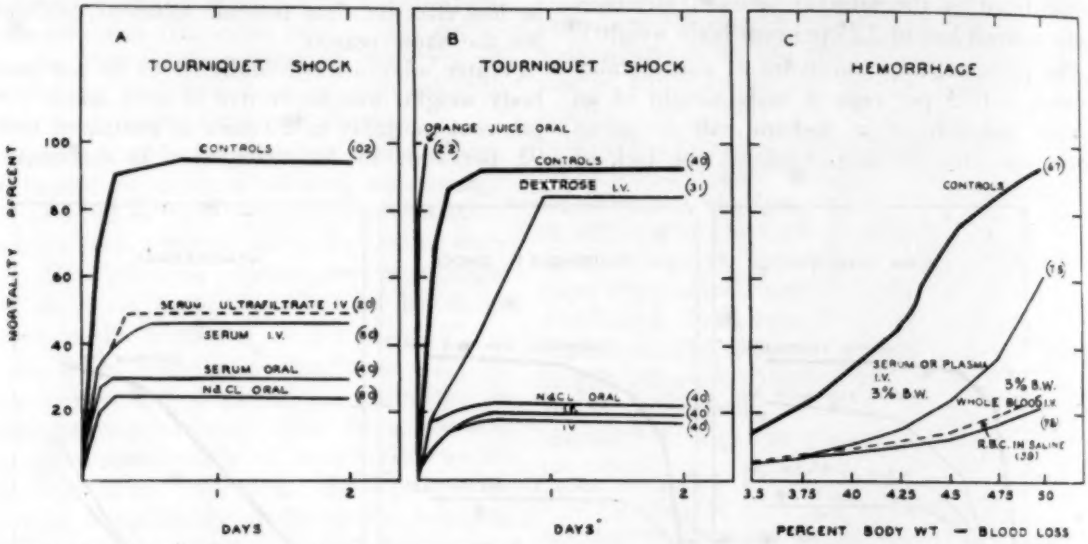

Chart 5.—*A*, the similar therapeutic response of mouse serum given orally and intravenously, a protein-free ultrafiltrate of serum administered intravenously, and 0.9 per cent solution of sodium chloride given orally in amounts of 8 to 10 per cent body weight. *B*, equal effectiveness of 0.9 per cent solution of sodium chloride given orally, intraperitoneally and intravenously and the slight effect of 5.5 per cent dextrose administered intravenously in amounts of 10 per cent body weight. The harmful effect of orange juice given orally in 5 per cent of body weight. *C*, the superiority of whole blood over serum or plasma in hemorrhage; equal effectiveness of whole blood and erythrocytes in saline solution. All curves are composite of results of several experiments, with the number of mice for each curve shown in parentheses.

THERAPY WITH SERUM, PLASMA AND WHOLE BLOOD

It is fundamental to the problem to recognize that in shock there occurs a disturbance of fluids and electrolytes in the blood and tissues, which if corrected as far as possible will result in a high percentage of survivals. The problem presents itself as to what additional therapy will prove of benefit.

There are other known factors, such as protein losses, anoxia, decreased blood volume, acidosis, infection and undoubtedly unknown ones, which may contribute to the mortality in shock. It is important to know whether such disturbances are primary or secondary and, if possible, to evaluate their influence on mortality by means of experimental therapy.

In burn or traumatic shock and in death from hemorrhage in the mouse, the therapeutic effect of serum or plasma could be accounted for by the amount of isotonic sodium which they contain. We have been unable to demonstrate an effect on mortality attributable to the administration of serum or plasma proteins. A comparison of certain amounts of mouse serum or plasma with equal quantities of isotonic saline solution has shown no significant difference in response in these three forms of trauma (chart 4).

A more exact analysis was attempted by comparing the electrolytes in serum with the original serum. This was accomplished by employing a

27. Shock Report 57, Committee on Medical Research, National Research Council, Feb. 9, 1945.

protein-free ultrafiltrate of serum along with the same serum and also by comparison of serum given by mouth (whereby the proteins as such would not be absorbed) with serum administered intravenously. In these experiments [28] likewise, the therapeutic response could be attributed to the electrolytes contained in the serum (chart 5 *A*). The results with serum albumin (human) were inferior to those with saline solution or serum and here, again, could be correlated with the amount of electrolyte solution (isotonic solution of sodium chloride) contained in the preparation (chart 4 *A*).

In contrast to the absence of influence of administration of serum protein was the better therapeutic effect observed in hemorrhage when whole blood or erythrocytes in isotonic solution of sodium chloride were compared with plasma or saline solution alone (chart 5 *C*).

We have carried out similar studies with whole blood therapy for traumatic and burn shock and were unable to demonstrate any superiority over plasma or isotonic solution of sodium chloride similarly administered. In tourniquet shock, treatment with whole blood, 5 per cent body weight intravenously, brought about a survival of 35 per cent of 32 mice while with plasma 40 per cent survived. In burn shock, similar treatment with whole blood resulted in 42 per cent survivals as compared with 66 per cent with plasma. Thirty to 32 mice were employed in each group, and the control mortalities (untreated mice) were 100 per cent in both experiments.[29]

It is thus observed that under these experimental conditions therapy with whole blood is of value in hemorrhage, but in burn or traumatic shock no superiority over plasma or saline solution could be demonstrated. These observations are of particular interest in view of the recent use of whole blood in the treatment of all forms of shock.

OTHER FACTORS

Brief mention will be made of some other factors which we have studied in shock. The harmful effect of an environmental temperature that is too hot or too cold is now well recognized [30]; the exact optimum remains to be established but available evidence indicates that it lies between 16 and 24 C.[30a]

Administration of 100 per cent oxygen at atmospheric pressure did not affect mortality of burn or tourniquet shock in mice [29]; Frank and Fine have previously reported negative results with oxygen at a pressure of 3 atmospheres for dogs.[31] Morphine in analgesic doses (2 to 6 mg. per kilogram) had no unfavorable influence on burn shock in mice [29]; Blalock has previously reported similar results in dogs.[32] Injection of adrenal cortex extract either prophylactically or subsequent to burns did not affect the acute mortality. Likewise, no therapeutic effect was observed from therapeutic doses of epinephrine in oil or from posterior pituitary extracts.[2b] In local therapy of burns, covering two thirds or more of the body surface with tannic acid, liquid petrolatum or cod liver oil was deleterious in that the mortality from shock was increased.[2a]

The immunity which has been observed after repeated trauma has been shown to be a local tissue response rather than a humoral reaction.[33]

COMMENT

With simplified procedures it has been possible to study the acute mortality following burns, trauma and hemorrhage in large numbers of small animals. The correction of disturbances of fluids and specific electrolytes has been demonstrated to be of greater importance for survival than the administration of plasma proteins. Our results indicate that for the most favorable response quantities of isotonic solutions of sodium salts equal at least to 10 per cent of body weight are indicated during the first twenty-four hours. In this respect, it is believed that current methods of treating shock are inadequate.

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by Environmental Temperature, Proc. Soc. Exper. Biol. & Med. **51**:350-351 (Dec.) 1942. Rosenthal.[2a] Ricca, Fink, Katzin and Warren.[14g]

30a. More recent studies of temperature effects [29] have shown that the increased survival time of untreated animals kept at 16 to 22 C. is not a true criterion of optimum temperature. When mice with tourniquet shock are treated with adequate amounts of isotonic solution of sodium chloride or plasma, an entirely different response is obtained; the majority of them will live if kept at 26 to 29 C., while the majority of them will die if kept below 22 C. or above 31 C.

28. Rosenthal.[3] Tabor, Kabat and Rosenthal.[4]

29. Unpublished results.

30. Gatch, W. D., and Wakim, K. G.: Effect of External Temperature on Shock: Experimental Study, J. A. M. A. **121**:903-907 (March 30) 1943. Cleghorn, R. A.: The Effect of Different Environmental Temperatures on the Survival of Dogs After Severe Bleeding, Canad. M. A. J. **49**:363-367 (Nov.) 1943. Elman, R.; Cox, W. M.; Lischer, C., and Mueller, A. J.: Mortality in Severe Experimental Burns as Affected

31. Frank, H. A., and Fine, J.: Traumatic Shock: V. A Study of the Effect of Oxygen on Hemorrhagic Shock, J. Clin. Investigation **22**:305-313 (March) 1943.

32. Blalock, A.: Effects of Morphine in Experimental Shock Due to Hemorrhage, Arch. Surg. **47**:326-328 (Oct.) 1943.

33. Rosenthal, S. M.; Tabor, H., and Lillie, R. D.: The Local Nature of Acquired Resistance to Trauma, Am. J. Physiol. **143**:402-406 (March) 1945.

Of practical importance is the fact that oral therapy is efficacious in the treatment of shock. The administration of these large volumes of isotonic saline solution can be accomplished most easily and with the least hazard if they are given in large part by mouth (or through stomach tube, if necessary). Such treatment can be carried out in in the absence of equipment for intravenous injections or trained personnel. However, for a patient in severe collapse or coma, when death may be imminent, when intestinal absorption may be slow or when, for any reason, oral medication is difficult, oral therapy alone should not be relied on and intravenous or other routes of administration should be given preference.

The experimental results would seem to justify clinical trial of oral electrolyte therapy for shock as a first aid or an emergency measure in civilian and military practice, since it can be employed under the simplest conditions and, when the emergency demands, can be adapted to self medication.

It should be emphasized that these observations are concerned only with the first forty-eight hours following injury and also that infections or other complications which may occur require individual attention.

SUMMARY AND CONCLUSIONS

The sodium, potassium and fluid changes have been studied quantitatively in traumatic shock in mice. The magnitude of these alterations and the high susceptibility of shocked animals to experimentally produced increases in these changes suggest that their combined effects may play an important role in the mortality from shock.

A high percentage of animals will survive an otherwise fatal burn, trauma or hemorrhage if isotonic solutions of sodium salts in amounts equivalent to 10 to 15 per cent of body weight are administered by any route during the first twenty-four hours. The effect of the electrolyte is a function of the sodium ion.

It is believed that current methods of treating shock are inadequate in regard to the quantity of isotonic sodium solution employed.

Experimental evidence indicates that this therapy may be of value as a first aid prophylactic measure, as well as in the treatment of shock, in military and civilian practice.

GELATIN SPONGE, A NEW HEMOSTATIC SUBSTANCE

STUDIES ON ABSORBABILITY

HILGER PERRY JENKINS, M.D., AND JAMES S. CLARKE, M.D.
CHICAGO

Hemostasis is a fundamental principle in surgical technic. It can be satisfactorily obtained in most instances by ligature, clips, pressure, electrocoagulation and packs. There are some situations, however, in which venous or capillary bleeding may be difficult to control by these methods. This is especially true of neurosurgical operations in which bleeding from the dura, the brain or the spinal meninges may be especially troublesome. This also obtains in many instances of general surgical procedures, such as operations on liver, kidney, spleen, pancreas, thyroid, bone, chest and female generative tract, in which conventional hemostatic methods may not be adequate. Ways and means of obtaining better hemostasis in such circumstances would constitute a substantial improvement in the general technic of surgery.

The major recent advances in the problem of control of capillary and venous oozing have been the development of coagulating agents, such as thrombin, and the use of absorbable substances which will aid in clot formation by purely mechanical means, such as transmitting pressure to the bleeding surface and offering a matrix for the formation of the clot. The clot-forming properties of these substances are presumed to be enhanced by the addition of the thrombin. The use of muscle stamps, which was introduced by Cushing [1] in 1911 and has been rather widely used in neurosurgical procedures since that time, constitutes the first general use of these principles, in that the muscle transmits some pressure, is absorbed and contains a clot-promoting substance.[2]

The work of Seegers [3] and his co-workers deserves special mention as a major contribution to the problem of hemostasis. They have developed a method of preparing a purified thrombin, which is now commercially available, and, furthermore, they have worked out a method of calibration and standardization of the potency of the thrombin known as the Iowa unit. There have been commercial preparations of thrombin or clot-promoting substances obtained from muscle or tissue extracts which have been available on the market for many years. This type of material has been outmoded, however, since the work of the Iowa group.

From the standpoint of absorbable substances which could mechanically aid in the formation of a clot, the work of Frantz [4] deserves attention. She found that oxidized cellulose in the form of absorbable cotton, paper or gauze was absorbed in eleven to thirty days in dogs and cats and produced only a mild foreign body reaction. She and co-workers reported the successful use of oxidized cellulose without thrombin to control bleeding in 17 cases in which muscle would otherwise have been required for hemostasis. Putnam [5] used oxidized cellulose soaked in thrombin to control bleeding in thirty neurosurgical operations and found it satisfactory. Cronkite, Deaver and Lozner [6] have been favorably impressed with the use of thrombin with and without oxidized cellulose to arrest hemorrhage in operative and traumatic wounds. The observations of Uihlein

From the Department of Surgery, University of Chicago, The School of Medicine.

This work was aided in part by a grant from The Upjohn Company, Kalamazoo, Mich.

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and colleagues [7] on the use of oxidized cellulose and thrombin has been favorable in 57 out of 60 cases at the Mayo Clinic.

One of the most significant contributions to hemostasis has resulted from the large scale plasma fractionation program conducted by the department of physical chemistry of the Harvard Medical School. One of the products of this fractionation of human plasma was fibrin foam, the cerebral cortex of monkeys. It was found that the foam soaked in thrombin had a hemostatic action, was absorbed and caused a minimum tissue reaction. They reported on its use in operations on 34 patients and felt that it had a number of advantages over muscle as a hemostatic agent. Woodhall [10] reported on the use of fibrin foam soaked in thrombin in 226 neurosurgical operations and found that a desirable

Fig. 1.—Gelatin sponge in liver after two days. The architecture of the sponge is well demonstrated. The interstices are partially filled with red blood cells, and at the junction with the liver there are a few polymorphonuclear leukocytes. There is no evidence of tissue reaction in the liver parenchyma.

which Bering [8] described in 1944. This material was tested by Ingraham and Bailey [9] in and on hemostatic effect was obtained. Fibrin foam has been available only in limited quantities and has been restricted in its use to a relatively small group, composed mostly of neurosurgeons.

7. Uihlein, A.; Clagett, O. T.; Osterberg, A. E., and Bennett, W. A.: Absorbable Oxidized Cellulose with Thrombin as a Hemostatic Agent in Surgical Procedures, Surg., Gynec. & Obst. **80**:470, 1945.

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10. Woodhall, B.: Fibrin Foam as a Hemostatic Agent in Rehabilitation Neurosurgery, J. A. M. A. **126**:469 (Oct. 21) 1944.

The most recent of the absorbable hemostatic materials is gelatin sponge or foam.[11] This is prepared from ordinary commercial gelatin, which is made up in a solution, to which a hardening agent is added. After bubbles of air are introduced, the mixture is allowed to dry in pans. It can then be cut into any desired size or shape. The material which has been used for experimental purposes has been provided in sealed glass jars previously subjected to sterilization with dry heat. The gelatin sponge is a white crisp material which is extremely light in weight. One cubic centimeter weighs 9 mg. The sponge will take up many times its weight of water when it is submerged and the air bubbles expressed. When moistened, the gelatin sponge shrinks and becomes soft and pliable. It easily adjusts itself to any irregularities in the surface to which it is applied. It does not fragment easily, although it is not especially tough.

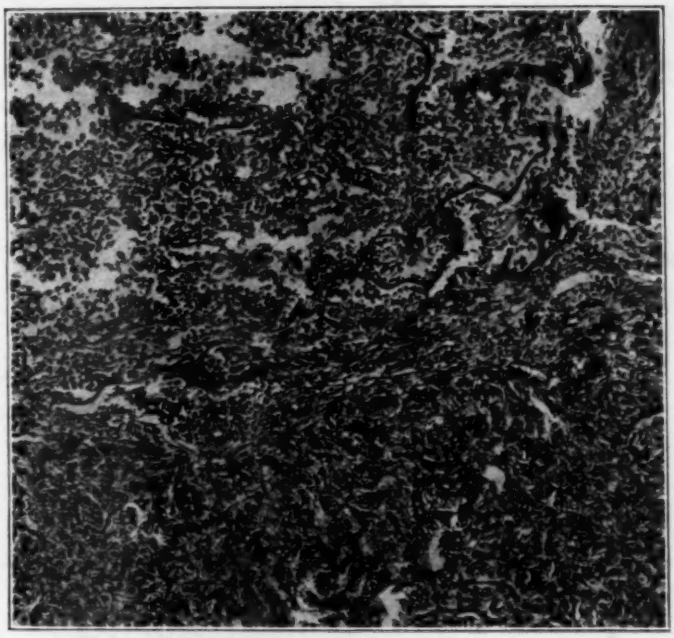

Fig. 2.—Gelatin sponge in liver after seven days. There is a wide zone of polymorphonuclear leukocytic invasion of the sponge at its junction with the liver, the parenchyma of which does not appear to exhibit any inflammatory reaction. The sponge appears to have undergone a considerable degree of absorption, as only fragments remain near the liver.

EXPERIMENTAL STUDY

An experiment was devised primarily to determine the behavior of the gelatin sponge in the tissues of animals and the response of the tissues to the gelatin. To avoid the introduction of an additional factor in this evaluation, the gelatin sponge was used without thrombin.

A series of 12 dogs was operated on by ordinary aseptic surgical technic with ether anesthesia. After the abdomen had been opened, incisions were made 2 cm. long and 1 cm. deep in the liver, the kidneys and the spleen. The brisk hemorrhage which resulted from these incisions was controlled by packing the moistened gelatin sponge into the incision and holding it in place for about two minutes with ordinary moistened gauze. When the gauze was removed, the gelatin sponge was usually adherent in the incision and the bleeding stopped. Sometimes there was oozing from the ends of the incision, which was arrested by laying another piece of gelatin sponge over the length of the incision and covering the previously applied sponge. Gelatin sponge was also implanted in the omentum and in the rectus muscle near the abdominal incision. The animals were killed at periods varying from two to fifty-six days after the implantation. Two of the animals died at two and three days respectively.

At autopsy the sponge could usually be easily identified in the short term implants as a red soggy mass. In the omentum there was an area of induration, in the center of which the sponge could be found if the omentum was cut across at this point. In the abdominal wall one could usually detect a small area of induration along the peritoneal surface (the sponge was put between the posterior sheath and the rectus muscle) which when cut revealed the sponge. After a week or ten days it was often difficult to

11. Correll, J. T., and Wise, E. C.: Certain Properties of a New Physiologically Absorbable Sponge, Proc. Soc. Exper. Biol. & Med. **58**:233, 1945.

identify the sponge in the abdominal wall, and in the omentum one could find only a slightly indurated area in which the sponge could be found. After two weeks it was difficult to identify the sponge grossly in the omentum. The sponge could usually be easily identified in the early specimens of liver, kidneys and spleen. Varying amounts of fibrinous adhesions were present about the implants in the liver, although such adhesions were not common in the kidneys or the spleen. Implants observed later showed evidence of fibrous adhesions of varying amount which completely covered any portion of the gelatin sponge. The sponge could be identified in these later specimens only by cutting through the thin layer of fibrous encapsulation, and even then one could not be sure of the presence of any residual gelatin sponge until the microscopic sections were inspected. This was especially true of the specimens in which the sponge had been implanted a month or more. In a few instances of short term implants in the liver, there was some evidence of exudate between the sponge and the surface of the liver.

Microscopic sections were made of all the implants which could be identified either grossly or as a residual fibrous adhesion. The gelatin sponge appeared as a meshwork of homogenous hematoxylin-staining material. Where the sponge had been used for hemostasis, as in the liver, the kidneys and the spleen, the interstices of the sponge were seen to be filled for the most part by red blood cells (fig. 1). In some sections there was evidence of invasion of the peripheral portion of the sponge by polymorphonuclear leukocytes. In the instances in which the polymorphonuclear invasion was especially noticeable, there was evidence of absorption of the gelatin sponge (fig. 2 and 3). In most sections,

Fig. 3.—Gelatin sponge in omentum after seven days. There is a gradual transition from the central portion of the sponge, where there are only a few invading cells, to the periphery, where there is invasion of the interstices by fibroblasts, polymorphonuclear leukocytes, lymphocytes and macrophages. There is a gradual disintegration of the sponge architecture at the peripheral part, which merges with a surrounding zone of cellular response similar to that seen within the interstices.

however, there was only a slight invasion of the sponge by polymorphonuclear leukocytes. In addition, there were also lymphocytes and some plasma cells in the peripheral portions.

After a week or more, the predominant cells invading the gelatin sponge were macrophages. There was little tendency for the formation of foreign body giant cells, such as one sees frequently in microscopic sections of suture material such as cotton, silk, linen or chromic surgical gut. These macrophages did not form a dense mass of cells, such as one sees at the site of absorption of chromic surgical gut, but rather a more evenly dispersed grouping of cells throughout the interstices of the sponge (figs. 4, 5 and 6).

Fibroblast response was usually observed within a week, producing a definite encapsulation of the sponge. Subsequently this encapsulation became fibrous. In the longer term implants, the fibrous tissue appeared to invade the periphery of the sponge where absorption had occurred as a result of the activity of the macrophages.

In some of the sections there was evidence of the surgical gut suture material which had been used to hold the implant in place. The tissue response to the gut was invariably more pronounced than that observed for the gelatin sponge.

Fig. 4.—Gelatin sponge in liver after twenty-three days. The gelatin sponge is separated from the normal-appearing liver cells by a thin zone of fibrous tissue which merges with and invades the peripheral portion of the sponge. The interstices of the sponge are filled with red blood cells in some areas, and there are a moderate number of macrophages throughout. Polymorphonuclear leukocytes are scarce. There is some thinning out of the walls of the cavernous spaces and some collapsing of the walls, indicative of a moderate degree of absorption.

The absorption of the gelatin sponge was apparently most rapid in the presence of polymorphonuclear leukocytes, which appeared to produce a liquefaction of the gelatin sponge. In some such instances, the absorption had progressed almost to completion within twelve days. On the other hand, most of the implants showed evidence of a slower absorption, which appeared to be carried out by macrophages and which

apparently required as long as five weeks or more to complete the absorption. It is probable that larger pieces of gelatin sponge may require a longer period than this to undergo complete absorption.

COMMENT

These experiments have demonstrated that gelatin sponge is a bland substance which is generally slowly absorbed in the tissues over a period of about five weeks. There is apparently some degree of encapsulation and replacement of the gelatin sponge with fibrous tissue during the process of absorption. In the presence of conspicuous numbers of polymorphonuclear leukocytes, the gelatin sponge is rapidly absorbed. This is a point which resembles to some extent the behavior of surgical gut in the tissues. In an extensive study of the absorption of surgical gut,[12] it was found that when gut was rapidly absorbed there was a conspicuous polymorphonuclear leukocytic response, which was apparently responsible for the absorption by a liquefaction process. On the other hand, gut which was relatively slowly absorbed was characterized by a slight initial leukocytic response and a subsequent fibroblast and macrophage response which encapsulated the gut and gradually disposed of it by the phagocytic action of macrophages. In the work on surgical gut, itwas found that the instances of conspicuous initial leukocytic response were apparently induced to a greater extent by chemical irritants in the tubing fluid [13] than by irritant properties inherent in the surgical gut. The occasional instances in these experiments on gelatin sponge in which there was a conspicuous leukocytic response were probably due to an inflammatory reaction from bacterial contamination of the wound. The usual observation of a negligible leukocytic response of the tissues to the gelatin sponge indicates that this is a bland substance which does not possess inherent irritant properties.

It was interesting to observe the mechanical hemostatic action of the gelatin sponge when it was inserted into bleeding incisions in the liver, kidney or spleen. It is probable that this hemostatic action is due to the enormous surface contacts between the blood and the myriads of cavernous spaces in the sponge which take up the blood from the oozing surface. In addition, there is the advantage of the transmission of pressure to the bleeding surface by a substance which does not have to be removed, thus avoiding the recurrence of bleeding so often experienced when one attemps to control the bleeding from an oozing surface by simple pressure of an ordinary piece of gauze, which must be ultimately removed.

Since there is little doubt about the effect of thrombin in promoting clot formation, wherever one wishes to obtain the maximum hemostatic effect one should probably combine the thrombin with the mechanical hemostatic agent. The extent to which the thrombin enhances the hemostatic action of the mechanical hemostatic agents has not as yet been clearly demonstrated. Experiments haye been planned which may clarify this point.

The clinical use of this gelatin sponge or foam to aid in the control of bleeding with or without the thrombin has an enormous number of possibilities. It would appear to be useful wherever fibrin foam or oxidized cellulose has been proved to be of value. It is not within the scope of this communication to evaluate the relative merits and limitations of these relatively new hemostatic substances; however, there is a place for some review of the situation from the observations thus far made.

Muscle is not a satisfactory hemostatic agent. It is not freely available without resort to an additional incision. Muscle is not so easily molded to irregular surfaces, and it causes appreciable tissue reaction. According to Ingraham and Bailey, oxidized cellulose is inferior to fibrin foam because its looser structure is less well adapted for hemostasis, it does not adhere to tissues as well and it cuts and molds less easily. Moreover, Seegers and Doub have shown that the carboxyl groups of oxidized cellulose rapidly inactivate thrombin solution unless neutralized with sodium bicarbonate beforehand. Although fibrin foam appears to have an advantage over oxidized cellulose, it is dependent for its production on a large scale program of collection and

12. Jenkins, H. P., and Hrdina, L. S.: Absorption of Surgical Gut (Catgut): I. The Decline in Tensile Strength in the Tissues, Arch. Surg. **44**:881 (May) 1942; II. Pepsin Digestion Tests for the Evaluation of Duration of Tensile Strength in the Tissues, ibid. **44**:984 (June) 1942. Jenkins, H. P.; Hrdina, L. S.; Owens, F. M., and Swisher, F. M.: Absorption of Surgical Gut (Catgut): III. Duration in the Tissues After Loss of Tensile Strength, ibid. **45**:74 (July) 1942. Jenkins, H. P.: Absorption of Surgical Gut (Catgut): IV. Recommendations for Absorbability and Digestibility Specifications, ibid. **45**:323 (Aug.) 1942. Dunham, C. L., and Jenkins, H. P.: Surgical Gut Tubing Fluid as a Tissue Irritant, Ann. Surg. **118**:269, 1943. Jenkins, H. P., and Dunham, C. L.: Irritant Properties of Tubing Fluids as a Factor in the Tissue Reactions Observed with Surgical Gut (Catgut), ibid. **118**:288, 1943.

13. Sinclair, J. A., and Douglas, B.: Local Implantation of Gelatin in Wounds, Arch. Surg. **49**:47 (July) 1944.

fractionation of human plasma. It is doubtful whether this source could ever fill the needs of surgeons except as a special material to be used sparingly by a few.

It is hoped that the gelatin sponge or foam may serve the same useful purposes as fibrin foam, as it can be produced in unlimited amounts from materials which are plentiful and cheap. This would make available to the entire membership of the surgical profession a new substance which can be of aid in controlling bleeding when other methods are not applicable.

sponge is apparently rapidly absorbed in the presence of an acute inflammatory reaction in which there is a dense polymorphonuclear leukocytic reaction. Foreign bodies of any type generally cause trouble in the presence of an acute inflammatory process, and it is of interest to know that gelatin sponge will undergo rapid "liquidation" in such circumstances. Thus may be avoided the development of a draining sinus down to the foreign material, which often occurs when the foreign substance is resistant to the action of leukocytes. On the other hand, if

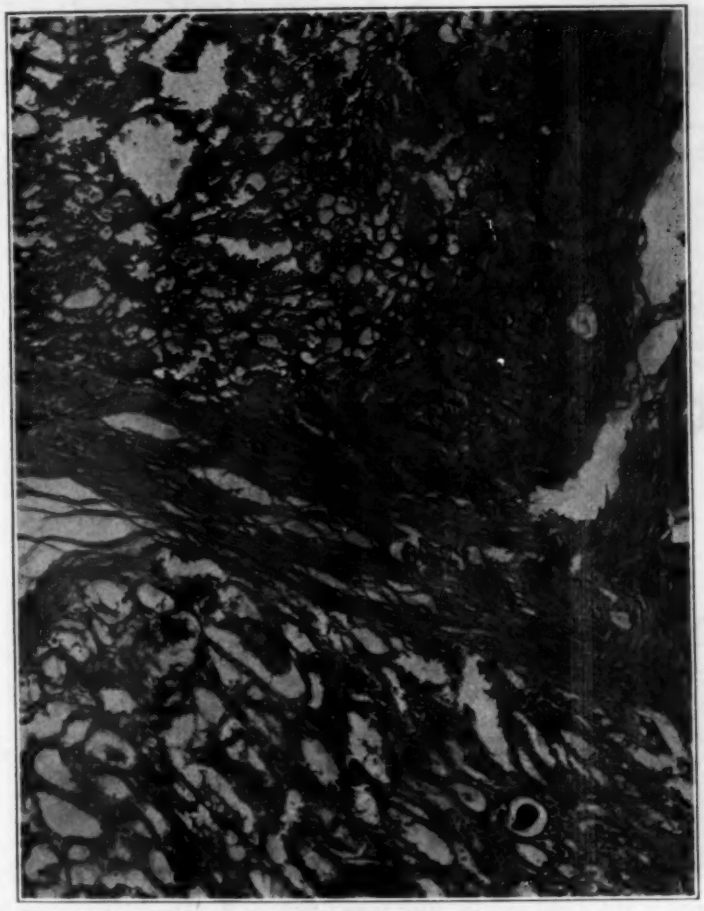

Fig. 5.—Gelatin sponge in kidney after twenty-three days. The gelatin sponge has a thin zone of fibrous tissue at the peripheral portion, which invades the interstices. This zone of fibrous tissue separates the sponge from the kidney parenchyma, which was incised at this point and appears to have healed in, extruding the sponge from the incision. There are red cells in some interstices. Some macrophages have invaded the sponge, which is undergoing a moderate degree of absorption. Cellular response in the section is less than that about most foreign bodies such as surgical gut, linen or silk.

Sinclair and Douglas [13] found that the local implantation of gelatin into wounds leads to an accelerated fibroplasia and increased strength. In the light of these findings, it may be that the gelatin sponge supplies a substance locally which is beneficial to healing of the wound. Another point which should be brought out is that gelatin there is no excessive leukocytic response to the sponge, it becomes incorporated in the tissues and gradually absorbed by a relatively mild phagocytic cell response.

The gelatin sponge has been used in 15 clinical cases in various ways to determine its behavior in human tissues. It has been used in

incisions in the liver to obtain specimens for biopsy, on the under surface of the liver after cholecystectomy, on thyroid beds after thyroidectomy, on dermatome donor areas, in laparotomy wounds and on the surface of granulating wounds. Our observations are too limited to permit us to draw any conclusions other than that bleeding was controlled and there were no complications which might be attributed to the use of the gelatin sponge. When the gelatin is used on granulating wounds, it undergoes absorption within a day or two. On dermatome donor areas, it usually undergoes absorption in a few days. The clinical and experimental observations thus far made lead us to believe that gelatin sponge could be considered for use in many situations other than neurosurgical operations. It would have a place in resections of bone in which there is troublesome bleeding from the bone. It certainly would be infinitely better tolerated by the tissues than bone wax. For resections of the liver, it would appear that this might offer a good supplement to suture and electrocoagulation technic. After cholecystectomy, one frequently encounters enough bleeding from the under surface of the liver that one hesitates to close the abdomen until the bleeding appears to be controlled. Suture of the under surface of the liver is a tedious procedure in some instances, especially when the relaxation of the abdomen is not good. Furthermore, one may sometimes create more bleeding by suturing over the raw liver surface than one had originally. This would be an especially suitable place for a hemostatic substance such as gelatin sponge. In gynecologic procedures, one may encounter oozing surfaces in the pelvis which are difficult to control by ligatures but which might respond to

Fig. 6.—Gelatin sponge in abdominal muscles after twenty-three days. The gelatin sponge has collapsed in some places and obliterated the interstices to some extent. The walls of the sponge structure are thin, and the interstices are invaded by fibroblasts, macrophages and lymphocytes in moderate numbers. The gelatin sponge appears to be in a moderately advanced stage of absorption. There is one area where a foreign body giant cell is noticed, which may be due to suture material rather than to sponge, as the gelatin does not appear to stimulate the formation of these foreign body type of giant cells.

this hemostatic substance. Bleeding from tooth sockets can be controlled by gelatin sponge.

The most hopeful use for the gelatin sponge might be as a first aid measure in military combat to pack into bleeding wounds when facilities are not available for the immediate treatment of the wounds. The use of a penicillin solution to moisten the sponge may have sufficient merit that it will be possible to control bleeding as well as infection until the patient is evacuated to a point where facilities permit more adequate care.

There is one point about gelatin sponge which must be considered, the fact that gelatin per se is an extremely good culture medium for bacteria and the introduction into contaminated wounds of a substance which would aid the growth of bacteria would not be without its limitations. It must be considered also that it is desirable to avoid or minimize the use of foreign material in a wound if possible. However, if one has the possibility of a troublesome hematoma to consider, there is justification for utilizing a substance which appears to present fewer hazards to the healing of the wound than a large hematoma.

SUMMARY

1. Gelatin sponge or foam was found to be a relatively bland substance which usually undergoes absorption by the phagocytic action of macrophages over a period of about five weeks.

2. The presence of a conspicuous number of polymorphonuclear leukocytes would generally lead to rapid absorption of the sponge within a few days to a week, by a liquefaction process.

3. The magnitude of the tissue reaction to the gelatin sponge during the period of absorption was generally less than that observed for surgical gut.

4. Gelatin sponge has a definite hemostatic action per se when applied to bleeding surfaces with moderate pressure.

CONCLUSIONS

Gelatin sponge or foam appears to have properties which make it suitable as an absorbable hemostatic substance and deserves clinical trial in the varied fields of surgery to further evaluate its merits and limitations.

BREAST CANCER AND "PAGET'S DISEASE OF THE BREAST"

CYRIL J. COSTELLO, M.D.

Trainee of the National Cancer Institute at Barnard Free Skin and Cancer Hospital

ST. LOUIS

This study, which has been prompted by the evidence of confusion and the divergence of opinion among clinicians and pathologists alike as to the nature of so-called "Paget's disease of the breast," embraces a thorough review of 29 cases[1] as well as a review of studies and observations by other investigators of this malady. The origin of this dissension emanates from confusion in regard to the cause and the significance of (and, consequently, the therapy indicated for) "Paget's disease." Here an attempt is made to answer the following questions: 1. What is "Paget's disease of the breast"? 2. Is there any cogent evidence as to its etiologic derivation? 3. How should it be treated? 4. Does the name "Paget's disease," which this malady has come to bear, actually clarify or confuse the picture, and is it, therefore, a justifiable eponym?

HISTORY

In 1874, Sir James Paget recorded in *St. Bartholomew's Hospital Reports:* "I believe it has not yet been published that certain chronic affections of the skin of the nipple and areola are very often succeeded by the formation of scirrhous cancer in the mammary gland. I have seen about fifteen cases in which this has happened, and the events were in all of them so similar that one description may suffice."[2] In this report Paget for the first time called attention to the malady which has since come to bear his name. He described a nipple and areolar eruption which was, he thought, not different from long persistent eczema, psoriasis or other chronic diseases of the skin. "But it has happened that in every case which I have been able to watch, cancer of the mammary gland has followed within at the most two years, and usually within one year."

Paget's description was based on clinical observations only, and it was not until two years later (1876) that microscopic study of the lesion was made by Henry Butlin.[3] He found changes in the galactophorous ducts but no actual cancer. The changes in the dermis he interpreted as eczema and concluded that the changes in the ducts were significant, inasmuch as, even though no cancer was discovered in the 2 patients that he described, it appeared highly suggestive that such might eventually have developed on the underlying duct and gland system. Butlin is generally and mistakenly credited with having been the first to describe the so-called "Paget cells," whereas, in reality, he does not mention these structures. It was in reality Darier, in 1889,[4] who for the first time recorded the description of the "Paget cell," the presence of which in the epidermis is characteristic of this disease. Darier proposed the view that the changes are the result of infestation by a "psorosperm" and that an epithelioma might ensue. The parasitic origin of the disease has since been abandoned as an etiologic factor. Thin, in 1881,[5] was the first to advocate that the lesion of the nipple may be secondary to a carcinoma of the underlying mammary gland.

In 1894 Unna[6] studied the peculiar intraepidermal cells and concluded that they were epidermal cells which had undergone a peculiar type of degeneration. In 1907 Winiwarter[7] claimed to have traced all stages in development from a prickle cell to a characteristic "Paget cell." In 1904 Handley[8] contended that the

From the Barnard Free Skin and Cancer Hospital; the Department of Surgery, Washington University School of Medicine.

1. From Barnard Free Skin and Cancer Hospital, Barnes Hospital and the St. Louis Jewish Hospital.

2. Paget, J.: On Disease of the Mammary Areola Preceding Cancer of the Mammary Gland, St. Barth. Hosp. Rep. **10**:87-89, 1874.

3. Butlin, H. T.: On the Minute Anatomy of Two Cases of Carcinoma of the Breast, Med.-Chir. Tr. **60**: 153-160, 1877.

4. Darier, M. J.: Sur une nouvelle forme de psorospermose cutanee: La maladie de Paget du mamelon, Compt. rend. Soc. de biol. **1**:294-297, 1889.

5. Thin, G.: On the Connection Between Disease of the Nipple and Areola and Tumours of the Breast, Tr. Path. Soc. London **32**:218-227, 1881.

6. Unna, P. G.: Die Histopathologie der Hautkrankheiten, Berlin, A. Hirschwald, 1894.

7. von Winiwarter, H.: Ueber Pagetsche Krankheit, Arch. f. Dermat. u. Syph. **85**:239-262, 1907.

8. Handley, W. S.: Paget's Disease of the Nipple, Lancet **1**:519-523 (April 7) 1917.

epidermal changes were "nutritional and non-malignant," resulting from filling of the corium and subcutaneous tissue lymphatics with cancer cells originating in the deeper ducts or acini.

In 1900 Darier [4] considered the characteristic Paget changes as due to "dyskeratosis." This view has since found a considerable following. According to Darier, dyskeratosis consists in developmental segregation in the epidermis of a number of malpighian cells, which subsequently develop in an abnormal manner, independent of their fellows. In this group of dyskeratoses he included Bowen's disease, dyskeratosis follicularis, Paget's disease and molluscum contagiosum.

Jacobaeus [9] in 1904 originated the view that the so-called Paget cell is from the first a malignant cell and that it represents an extension into the epidermis from underlying glandular carcinoma. Cheatle in 1923 and in 1930 [10] concluded that changes in the epidermis might result from carcinoma originating in different foci and that the origin must be determined separately in each case.

In 1927 Sir Robert Muir [11] further elaborated the view of Jacobaeus. Through his studies Muir was able to demonstrate that in his material "Paget's disease" was consistently associated with changes in the ducts. These changes varied from hyperplasia to intraductal types of carcinoma. He defined a "Paget cell" as a mammary cancer cell growing within a non-neoplastic epidermis.

CLINICAL CHARACTERISTICS

What has been called "Paget's disease of the breast" begins as an intractable eczema of the nipple or areola (fig. 1). The patient's first recollection of the onset is an often recurring pruritis of the skin in this region. Again, the first symptom may be a simple crust associated with weeping or even bleeding of a minor character when it is removed. In some instances the first bleeding is noted to come from the summit of the nipple, though this may not correspond with the center of the cutaneous lesion. In any event the cutaneous lesion fails to respond to treatment with simple ointments or protection from irritating clothing and often alternates for long periods between weeping and drying with crust formation.

The ages of the patients studied in this series varied, but all patients were past 30. There was no decade which had a preponderance of the cases, though 22 of the 29 patients were between 40 and 70 years when first seen. The duration of the cutaneous lesion before the patient consulted a physician varied within broad limits (table 2), but the preponderance of the patients here observed had noted a lesion on the skin for from one to three years previously. Three of the patients had noted a cutaneous manifestation for two weeks, thirty-five years and forty years respectively. The cutaneous lesion when ulcerated is usually bright red and inflamed, with a velvety surface of fine granular material. This may be small, or it may be extensive, with complete destruction of the nipple and involvement of the entire areola and contiguous cutaneous surface.

TABLE 1.—*Age Distribution of Patients*

Age Periods, Yr.*	Number of Cases
31 to 40	3
41 to 50	7
51 to 60	8
61 to 70	7
71 to 78 †	4

* The youngest patient was 31 years.
† The oldest patient was 78 years.

TABLE 2.—*Duration of Cutaneous Lesion*

	Cases, No.
Less than one month	3
One month to one year	12
One year to two years	6
Two years to three years	3
Three years to four years	2
Forty years	1
Thirty-five years	1
Unknown duration	1

The patients in some instances complain also of a lump in the breast; though frequently one may be discovered which has escaped the notice of the patient. In this series 17 patients (59 per cent) presented a demonstrable breast mass while 12 (41 per cent) had no grossly evident mass (table 3). Clinically, any eczema of the breast should arouse suspicion, and any such lesion which does not completely respond in a period of two weeks to conservative therapy with a

TABLE 3.—*Mass Palpable in Breast Affected*

	Cases, No.	Cases, %
Yes	17	59
No	12	41

9. Jacobaeus, H. C.: Paget's Disease und sein Verhältniss zum Milchdrüsenkarzinom, Virchows Arch. f. path. Anat. **178**:124, 1904.

10. Cheatle, G. L., and Cutler, M.: Tumors of the Breast, Philadelphia, J. B. Lippincott Company, 1930.

11. Muir, R.: Paget's Disease of the Nipple and Its Relationships, J. Path. & Bact. **30**:451-471 (April) 1927.

Fig. 1.—A characteristic picture of secondary epidermal carcinoma of the breast ("Paget's disease"). There is seen here thickening of the epidermal layer. In the corium is a capillary network as well as a moderate chronic inflammatory cellular infiltration. There are present in the epidermis abnormal large cells with neoplastic qualities and a surrounding clear zone (× 140).

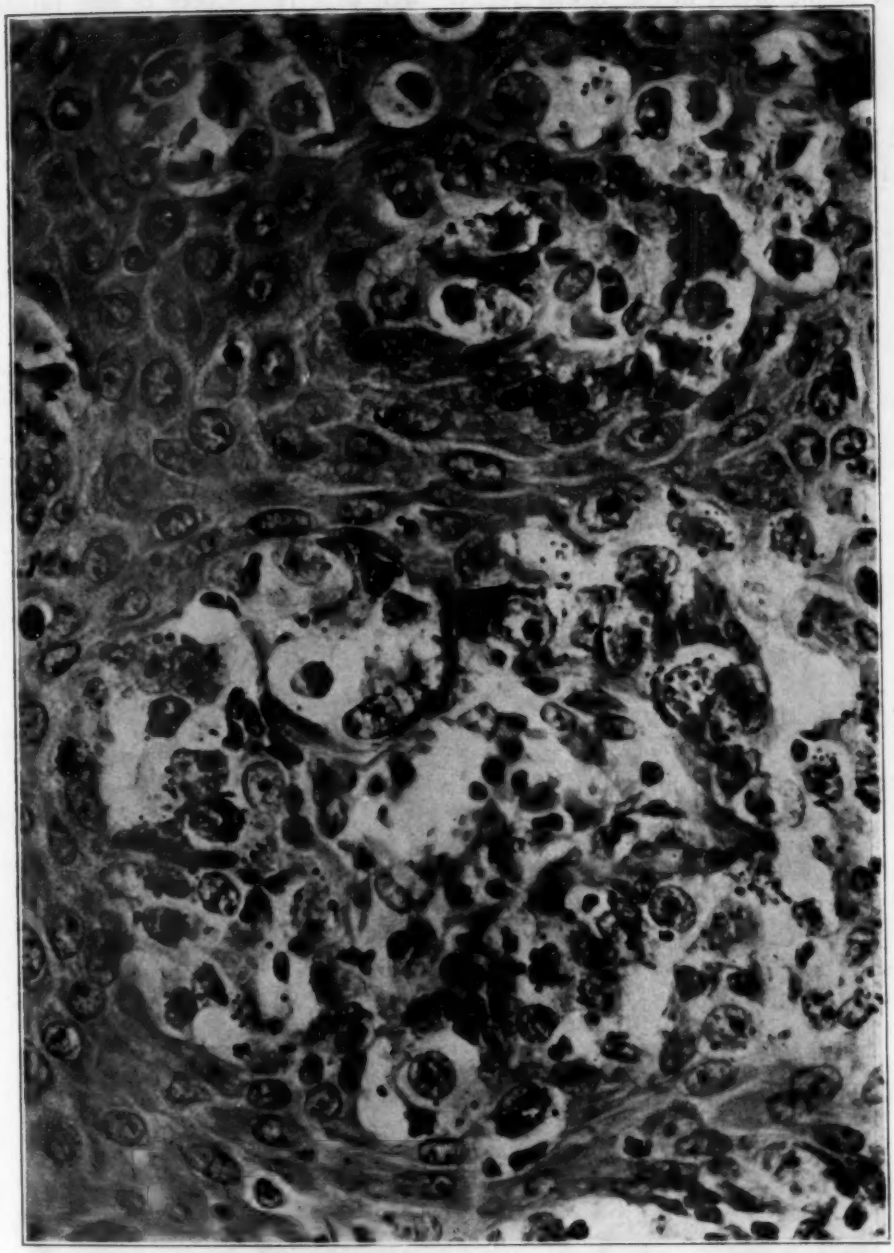

Fig. 2.—A view of the epidermis from a case such as that seen under lower magnification in figure 1 ("Paget's disease"). Here one sees the intraepidermal malignant cells dispersed singly and in bizarre clusters among the epidermal cells. Note that the neoplastic cells ("Paget cells") are generally large and have clear cytoplasm and pyknotic nuclei, and in no instance can be demonstrated intercellular bridges between the abnormal cells and the epidermal cells. The latter characteristic is in favor of the theory that the abnormal cells do not arise in the epidermis. Note also, in this regard, that the contiguous epidermal cells are displaced and compressed by the growth of the neoplastic cells (× 400).

bland ointment and protection from clothing that might be irritating should be subjected to biopsy.

PATHOLOGY

The characteristic part of the picture is found in the skin of the breast in the areolar region (fig. 2). The malpighian layer is usually thickened, and the rete pegs are elongated and broadened. The basal cell layer remains intact in most instances, though occasionally it is distorted, destroyed or only partially invaded by the "Paget cells." The corium contains a dense infiltration of lymphocytes and plasma cells as well as a rich supply of tiny capillaries. The most striking and the only consistent and sine qua non feature of this microscopic picture is the presence in the epidermis of a large neo-

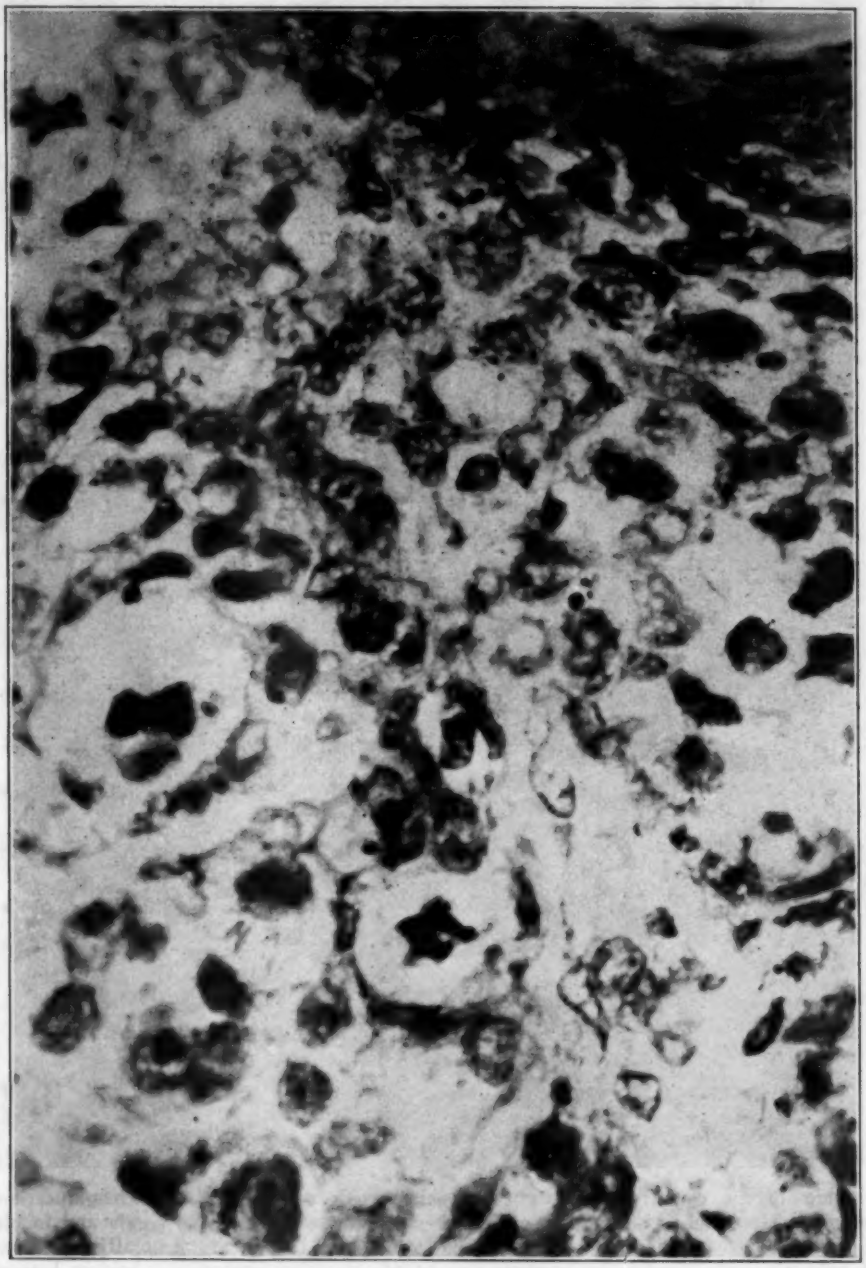

Fig. 3.—A mitotic figure appearing in an intraepidermal metastatic cancer cell ("Paget cell"). Such mitoses and other characteristics of neoplastic cellular patterns are typical of these cells (× 700).

plastic cell, the so-called Paget cell. This cell varies in size and other characteristics, just as any neoplastic cell might in any other locus. It is usually round or ovoid. Its nucleus is hyperchromatic, and mitotic figures are occasionally seen (fig. 3). The cells may occur singly or in bizarre clusters. The adjacent epidermal cells are often distorted by compression or hydropic degeneration (fig. 2). Characteristically, this neoplastic cell is surrounded by a clear space, and in no instance are intercellular bridges found to exist between it and the prickle cells. This picture must be differentiated from (1) Bowen's disease, (2) superficial epitheliomatosis, (3) simple eczema of the nipple and (4) squamous cell carcinoma of the breast.

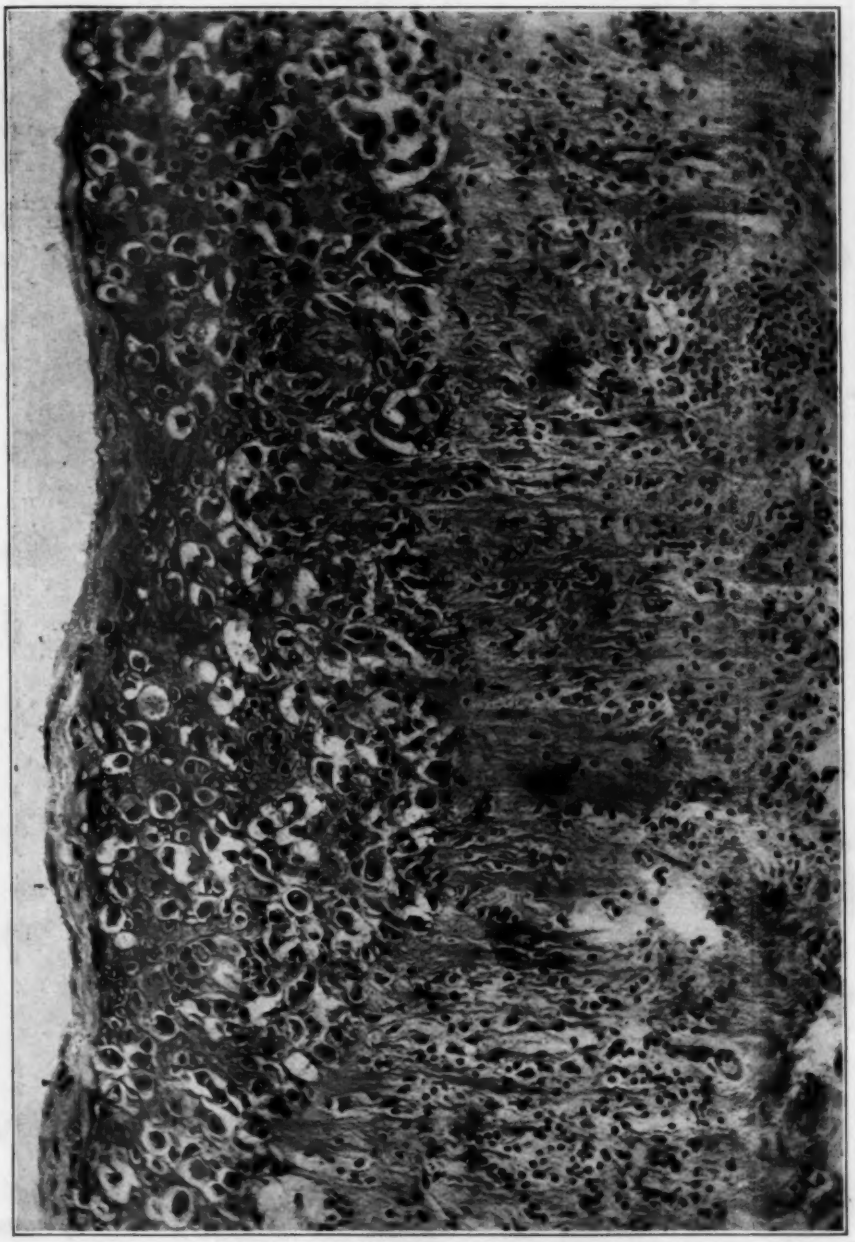

Fig. 4.—Bowen's disease of the skin. Here, again, the characteristic feature of the microscopic picture is the presence in the epidermis of abnormal cells. The Bowen cells, though large, have much intracellular edema and eccentrically located nuclei. Multinucleated cells are common and are spoken of as "basket cells." Hyperkeratosis as seen here is a frequent accompaniment of this lesion, while it is absent in intraepidermal mestastasis ("Paget's disease") (× 140).

1. *Bowen's Disease.* — Certain resemblances exist between Bowen's and "Paget's" diseases (fig. 4). Generally, Bowen's disease is considered to be a primary epithelial malignant growth of low grade and slow progression.[12] The characteristic feature is a large intraepidermal cell. This cell has a vacuolated cytoplasm and a small, deformed, shrunken nucleus, which is displaced to one side.

Also present in the epidermis are larger, multinucleated cells, the so-called basket cells. Intercellular edema is slight or not present at all in Bowen's disease, while it is often abundant in "Paget's disease." The chief distinguishing feature is that which would be expected in a con-

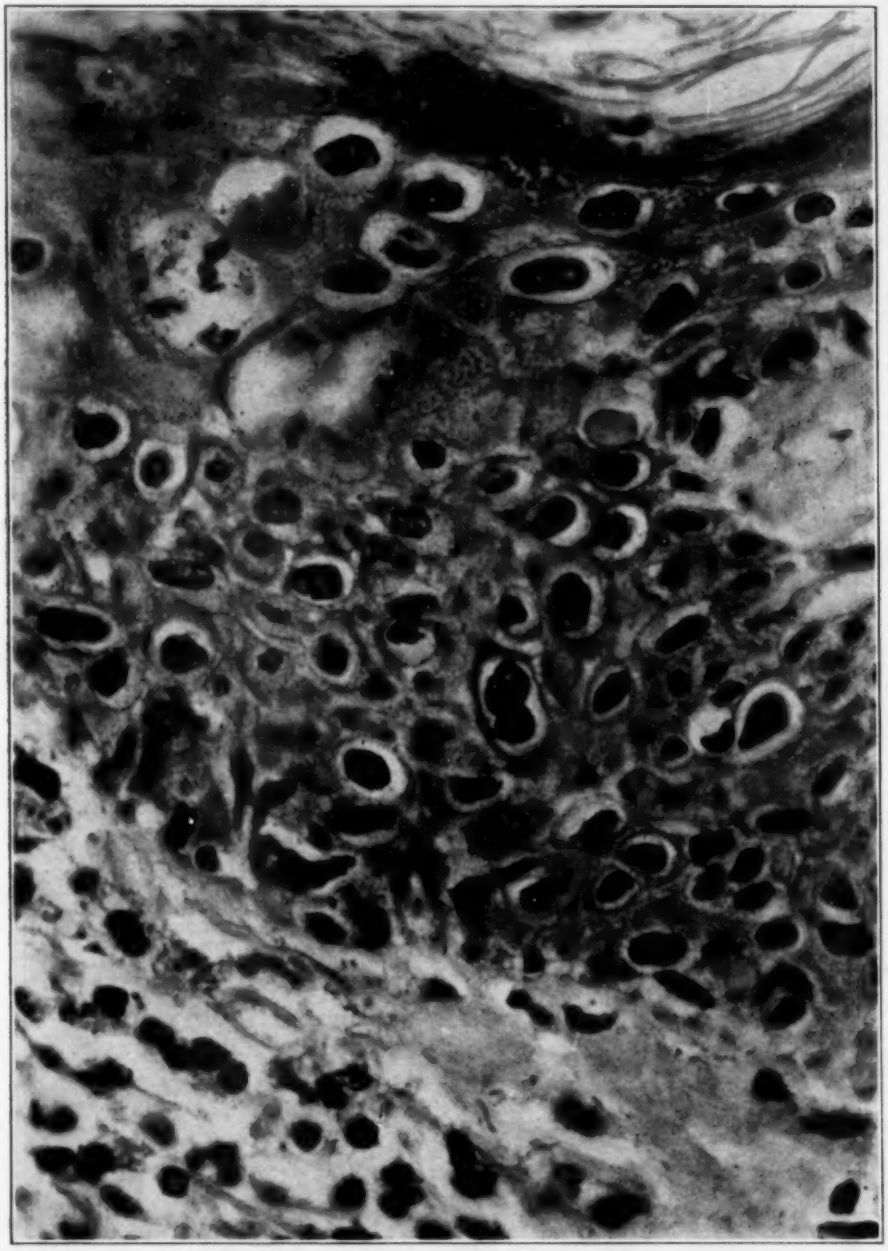

Fig. 5.—A higher magnification of the epidermis of Bowen's disease. The Bowen cells again present the characteristics of malignant cells (irregular size and shape, pyknotic nuclei and multiple nuclei) although there can be seen intercellular bridges extending between the Bowen cells and the adjacent epidermal cells. This is an indication that the neoplastic cell probably evolved from an epidermal cell. This presence of intercellular bridges can never be found in "Paget's disease," this fact furthering the evidence against the theory that "Paget cells" arise from epidermal cells (× 400).

12. Herold, W. C., and Cooper, Z. K.: Bowen's Disease: An Intra-Epidermal Carcinoma, S. Clin. North America **24**:1033-1043, (Oct.) 1944.

TABLE 4.—*Summary of Data in 29 Cases of Cancer of the Breast*

...ted cytoplasm ...ucleus, which ...larger, multi- ...cells. Inter- ...sent at all in ...in present the ...although there ...cells. This is ...of intercellular ...e theory that ...abundant in ...guishing fea- ...ted in a con-

TABLE 4.—*Summary of Data in 29 Cases of Cancer of the Breast*

Case	Age, Yr.	Duration Cutaneous Lesion	Palpable Mass	Clinical Picture	Pathology	Course
1	45	2 yr.	Yes	Two years ago patient taped both nipples with adhesive tape; right nipple became irritated and has refused to heal; nipple discharged serum and has been seat of constant pruritus; lump present in right breast many years Examination: Right nipple denuded, with raw, moist, bleeding surface; 2 in. (5 cm.) above right nipple is indefinite 1 in. (2.5 cm.) nodule; no nodes palpable	Adenocarcinoma of breast, with continuity of carcinoma cells in dermis into epidermis; in addition to intraepidermal extensions, ulceration and chronic inflammatory reaction found	Cutaneous lesion treated with petrolatum dressing for 6 wk., with no improvement; 10/6/39, radical mastectomy performed; 8/22/44, no recurrence demonstrable
2	56	?	No	Patient's mother had carcinoma of the breast; patient scratched by kitten; pruritic and bleeding lesion ensued; no response to treatment with ointment; 40 per cent of areola ulcerated and crusted; no nodes palpable	Intraductal carcinoma and intraepidermal malignant cells (Paget); no metastasis to lymph nodes	Biopsy of nipple revealed "Paget's disease"; 11/29/38, radical mastectomy performed; 9/15/44, no recurrence demonstrable
3	54	3 wk.	Yes	Patient aware of lump in left breast for 30 yr.; 3 wk. ago small ulcer developed at dome of left nipple, with no bleeding from lesion or nipple; nipple is verrucous, with crusted, 8 cm. ulcer; palpable mass deep in outer lower quadrant, which is not attached to the skin	Adenocarcinoma of breast and intraepidermal metastasis (Paget's disease of the skin)	10/26/37, simple mastectomy performed, physician believing patient had "cystic disease and keratosis of nipple"; 12/3/37, radical excision of remainder completed; 11/22/44, no recurrence found
4	61	1 yr.	No	Patient noted encrusted lesion at tip of left nipple for 1 yr.; "gradually becoming worse" Examination: Reveals such a lesion measuring 4 sq. cm.	(1) Typical "Paget's disease of nipple"; (2) adenocarcinoma of breast, with extensive axillary metastases	(1) 7/30/37, lesion and entire nipple excised; 3/18/38, 3 cm. hard mass in scar and 1 cm. soft node in left axilla discovered; (2) 4/1/38, radical mastectomy performed on left side; 11/11/40, patient died from generalized carcinomatosis
5	76	3 yr.	No	For 3 yr. patient had pruritus and burning of right nipple, also ulceration of nipple, with periods of healing Examination: Nipple eroded away by 6 cm. ulcer; no nodes palpable	Intraductal carcinoma; duct lined with malignant cells extends to skin of nipple and becomes continuous with intraepidermal invasion by malignant "Paget" cells	Simple mastectomy performed (because of patient's age) 7/13/33; 3/17/43, no recurrence
6	61	1 yr.	Yes	One year ago patient observed skin of left nipple "peeling off"; this continued, with no pain or discharge Examination: 2 cm. soft, pink excoriated left nipple; deep in breast tissue in upper outer quadrant is 3 by 4 cm. irregular mass	Biopsy reveals typical intraepidermal malignant cells, with intact basal cell layer; ductal carcinoma in underlying breast ducts	7/28/45, radical mastectomy performed on left side
7	46	6 mo.	Yes	Exuding ulcer of left breast present for 6 mo. Examination: Superficial erosion of left nipple; subjacent to nipple is irregular hard mass fixed to the skin; hard, movable node palpable in left axilla	Adenocarcinoma of breast and at epidermal margin, adenocarcinoma extensions; also in these zones are intraepidermal extensions of same cells, yielding the typical picture of "Paget's disease"	8/11/44, radical mastectomy performed; 12/6/44, no evidence of recurrence
8	45	20 mo.	Yes	Patient discovered induration and pain around right nipple 20 mo. ago; some bloody discharge associated with this Examination: Half of nipple excoriated and granulating; hard fixed subjacent mass palpable in breast	Adenocarcinoma of breast in continuity with epidermal picture of "Paget's disease"; some extensions of malignant cells can be traced into epidermis, in which they appear as "Paget cells"—actually malignant cells	12/8/39, radical mastectomy performed; no recurrence found when patient was last seen, 4/19/40
9	59	5 mo.	Yes	Five months ago patient noted her clothing adhering to left nipple; crust formed, with occasional bloody discharge; small lump noted at same time, which has increased slightly in size Examination: 7 cm. crusted ulcer on left nipple; subjacent to it is 1 cm. mass; 1 cm. hard node palpable in left axilla	Adenocarcinoma of breast with lymph node metastases; nipple lesion presents typical picture described as "Paget's disease," with resemblance of "Paget cells" to carcinoma cells of breast	8/9/40, radical mastectomy performed on left side; in 1942 patient died of hypertension
10	46	8 wk.	No	Eight weeks ago patient noted small red spot on left nipple; has had some pruritus	Adenocarcinoma of left breast and changes characteristic of "Paget's disase" in skin of nipple	12/30/40, simple mastectomy performed on left side; 12/30/42, no recurrence; patient not seen since

TABLE 4.—*Summary of Data in 29 Cases of Cancer of the Breast—Continued*

11	47	3 mo.	No	Three months ago patient noted small ulcer on right nipple; failed to improve with application of ointment at home	Adenocarcinoma of breast and no disturbance in basal layer of the epidermis; however, intraepidermal cells of "Paget" are typical malignant cells similar to those of the cancer of breast	11/8/40, radical mastectomy performed on right side; 9/19/44, no recurrence
12	48	2 yr.	Yes	Two years ago patient noted pruritus and small red "bump" on right nipple; subsequently, similar nodules appeared in skin of breast and have progressively grown larger Examination: Skin of right breast involved with multiple small, hard nodes as far as the midline anteriorly and posteriorly; large, hard mass at nipple, with surface crater, palpable	Adenocarcinoma of breast and intraepidermal cell clusters of malignant cells	4/5/17, shoulder girdle amputation and radical mastectomy performed; 4/9/17, patient died
13	66	3 yr.	Yes	Three years ago patient noted pruritus and crusting of right nipple; 3 mo. ago she noted lump in right breast Examination: Velvety, 2 cm. superficial ulceration of right nipple concentric with nipple; no definite mass discernible in breast by examining physicians	Adenocarcinoma of right breast with axillary metastases; changes in skin of nipple are typical of "Paget's disease," i. e., intraepidermal secondary malignant cell deposits	5/9/41, radical mastectomy performed on right side; 11/4/42, no recurrence evident
14	62	6 mo.	No	Small superficial ulcer on right nipple noted for 6 mo.; intermittent bleeding from nipple observed for same duration	On multiple sectioning of right breast, in upper inner quadrant was found 2 cm. hard mass; microscopic examination reveals adenocarcinoma with axillary metastases; nipple skin reveals picture of "Paget's disease," and intraepidermal cells appear to be malignant cells which have invaded epidermis	7/25/41, radical mastectomy performed on right side; 9/19/44, no recurrence evident
15	37	2 yr.	No	Two years ago discharge from left nipple developed; crust formed; when it separated, it left an ulcer, which later gradually enlarged; a few months ago tiny bumps formed over skin of breast; all lesions pruritic; no mass in breast and no palpable nodes in axilla	Adenocarcinoma and axillary metastases; lymphatics of dermis filled with adenocarcinoma; varying stages of extensions into epidermis; in other portions are intraepidermal clusters and single malignant cells; typical "Paget's disease of the skin"	1/24/18, radical mastectomy performed on left side; no follow-up
16	74	35 yr.	Yes	Patient has had eczematous lesion of right nipple for 35 yr.; nodule noted in right breast 4 yr. ago; it has slowly enlarged Examination: Superficial ulcer of entire right breast, with 3 cm. palpable mass in breast and palpable node in axilla	Biopsy 10/13/44: typical "Paget's disease of the nipple," with intraepidermal malignant cell invasion	Patient refused operation; 10,000 units of roentgen radiation given to tumor, after which entire process cleared; no mass and no eczema; in 4 mo. eczema reappeared and was more extensive; biopsy repeated; 12/26/43, patient died from carcinoma of the breast
17	42	4 yr.	Yes	Four years ago patient squeezed wartlike excresence from left nipple; 3 yr. ago she noted exudative lesion on that nipple Examination: Superficial ulcer of nipple and areola and 5 cm. mass movable in outer lower quadrant	Firm tissue deep to nipple contains duct carcinoma; in one section duct with carcinoma can be traced to epidermis; continued into epidermis by malignant invasion; also dermal invasion	11/11/42, radical mastectomy performed; 11/29/44, no recurrence demonstrable
18	53	1 yr.	Yes	One year ago patient noted sore on left nipple, which alternated a few days of healing and breaking down, with discharge; 9 mo. ago lump to left of nipple noted Examination: Left nipple retracted, broadened and superficially ulcerated; mass 4 by 3 cm. to left of nipple palpable but not fixed to skin or wall of chest	Adenocarcinoma of breast, with changes in skin characteristic of "Paget's disease"; again intraepidermal cells present characteristics of neoplastic cells in benign epidermis	2/25/44, radical mastectomy performed on left side; 11/17/44, patient died of generalized carcinomatosis
19	62	40 yr.	No	Patient noted small bleb on left nipple 40 yr. ago, which 4 yr. ago began enlarging Examination: Two shallow ulcers on left areola; no mass or palpable nodes present	Intraductal carcinoma with intraepidermal malignant cells identical with those in the duct neoplasm in typical "Paget's disease of the skin"	4/16/41, radical mastectomy performed; no follow-up
20	64	11 mo.	Yes	Patient had radical mastectomy of left breast in 1925 for carcinoma; pruritus and recurring scaling of right breast present for 11 mo. Examination: Nipple absent, and areola white, indurated and depressed; nodule palpable just under areola in breast	Adenocarcinoma of breast; typical "Paget's disease of nipple skin"	12/6/37, radical mastectomy performed; no follow-up

TABLE 4.—*Summary of Data in 29 Cases of Cancer of the Breast—Continued*

		Duration	Cutaneous	Pal			

20	64	11 mo.	Yes	Patient had radical mastectomy of left breast in 1925 for carcinoma; pruritus and recurring scaling of right breast present for 11 mo. Examination: Nipple absent, and areola white, indurated and depressed; nodule palpable just under areola in breast	Adenocarcinoma of breast; typical "Paget's disease of nipple skin"	12/6/37, radical mastectomy performed; no follow-up

TABLE 4.—*Summary of Data in 29 Cases of Cancer of the Breast—Continued*

Case	Age, Yr.	Duration Cutaneous Lesion	Palpable Mass	Clinical Picture	Pathology	Course
21	31	2 yr.	No	Pruritus of right nipple present for 2 yr.; in recent months small, exuding ulcer of nipple developed, with occasional bleeding Examination: Excoriation, with serosanguinous weeping of nipple; no mass or palpable nodes discernible	Intraductal carcinoma; in one focus can be seen invasion through wall of a duct; typical "Paget's disease of skin," with close resemblance of intraepidermal and intraductal malignant cells	6/7/44, radical mastectomy performed on left side; 1/30/45, no evidence of recurrence
22	69	18 mo.	No	For 18 mo. patient noted chapping and cracking of right nipple with pruritus; slow enlargement of lesion Examination: 6 mm. superficial ulcer of right nipple, with induration of entire nipple; no palpable mass found; two small, movable nodes present in each axilla	Adenocarcinoma with lymph node metastases; sections demonstrate nests of adenocarcinoma at basal cell layer of epidermis, with "Paget cells" in adjacent epidermis—identical with carcinoma cells; also lymphatics in derma containing carcinoma cells	6/5/43, radical mastectomy performed on right side; 2/2/45, no recurrence found
23	59	3 yr.	Yes	Three years ago patient noted white film over right nipple, with a pinhead hole in its center; crust and discharge followed, and slowly nipple eroded away; 4 mo. ago patient noted mass in upper part of breast Examination: 8 cm. mass, movable in upper part of breast; nipple is eroded away, with replacement by dirty ulcer	In some sections are adenocarcinomatous arrangements in dermis extending to basal cell layer; in others is direct extension into epidermis; duct also seen, lined with malignant epithelium; these cells identical with intraepidermal malignant cells ("Paget")	5/1/41, simple mastectomy performed; 11/23/44, patient died at city sanatorium with a "psychosis"
24	78	3 wk.	Yes	In 1939, patient had mastectomy and axillary dissection on right for carcinoma of breast; 10 mo. ago lump noted in left breast and left axilla; for 3 wk. soreness and crusting of left nipple noted Examination: Left nipple enlarged, ulcerated and crusted; 5 cm. hard mass palpable in lower outer quadrant of left breast, and four hard nodes found in left axilla	Breast adenocarcinoma and 'Paget's disease of skin"	5/27/43, axillary dissection and radical mastectomy performed on left side; 7/30/44, lump in right axilla; 8/1/44, axillary dissection performed on right side
25	58	6 mo.	Yes	Small excoriation on right nipple noted 6 mo. before, which alternated with crusting and oozing serum; discharge from nipple for 2 mo. Examination: 3 by 4 cm. ulcer of right nipple, with sharp margins, seen; retraction of nipple pronounced	Deep to the ulcer is 2 cm. mass containing ductal carcinoma; in one section is duct lined with malignant cells identical with "Paget's cells" seen in adjacent epidermis	2/12/36, simple mastectomy performed on right side
26	33	2 yr.	Yes	Left radical mastectomy performed 10 yr. ago for carcinoma; white discharge from right nipple, with crusting of skin, present for 2 yr.; patient noted mass in right breast 2 wk. ago Examination: Retracted right nipple, with white discharge and crusting of nipple skin; 2 cm. mass present in upper outer breast quadrant; it is not attached to the skin; hard mass palpable in right axilla	An adenocarcinoma with axillary metastases; changes in skin typical of "Paget's disease"; in one section is duct filled with malignant cells, and at ampulla the continuity of extension of duct neoplasm with that of epidermis can be traced as they are seen to invade the epidermis at the margin of the ampulla epithelium	7/7/38, radical mastectomy performed on right side; 11/24/41, small shot-sized node presented in right side of neck; intractable headaches, vomiting and progressive paralysis of right arm developed; 1/10/42, patient died
27	50	4 wk.	Yes	Small lump in each breast present for 4 wk. Examination: Each nipple retracted, with leathery mass subjacent to and attached to nipple	Adenocarcinoma in each breast; in the skin is typical picture of "Paget's disease"; malignant cells found in the dermis, extending into the epidermis; also in epidermis are multiple epidermal cells in state of hydropic degeneration	12/3/41, bilateral simple mastectomy performed; no follow-up
28	58	?	Yes	Mass in right breast noted 1 yr. ago; gradually increased to about three times its original size Examination: Retraction of skin of nipple; an orange-sized mass in outer lower quadrant of right breast attached to skin	Adenocarcinoma of breast, with extension into all layers of skin and ulceration in one zone; in margins of ulcerated zone are two abnormal cell types in epidermis: epidermal cells with hydropic degeneration and malignant cells identical with those in corium and breast tissue; latter are characteristic "Paget cells"	10/27/31, right radical mastectomy performed; 9/5/32, patient died of undetermined cause
29	68	6 mo.	No	Eczema-like eruption around right nipple present 6 mo. and failed to heal or improve with applications of ointments	Ductal carcinoma of the breast found, and some ducts filled with carcinoma cells traced to the epidermis, in which was a typical intraepidermal metastasis (Paget's disease)	5/11/45, simple mastectomy performed

sideration of the two different processes involved in pathogenesis. This is that in "Paget's disease" there is actual dissociation of the abnormal cell, whereas in Bowen's disease the cell continuity with adjacent epidermal cells is retained

2. *Superficial Epitheliomatosis.* — Superficial epitheliomatosis [13] may be of squamous cell or basal cell origin or mixed in character. It differs from the ordinary primary epidermal malignant neoplasm in that the malignant invasion extends

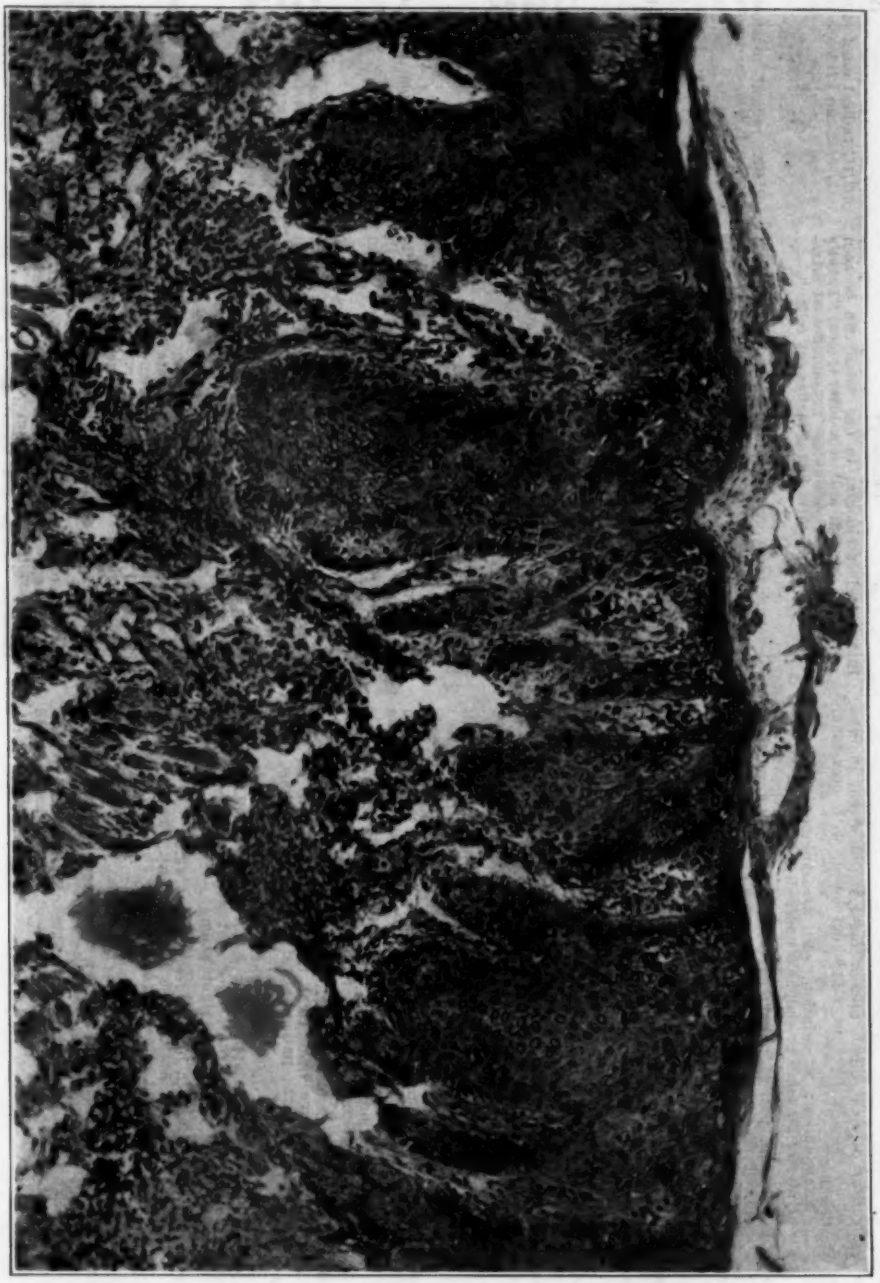

Fig. 6.—Chronic eczema. Here the picture is obviously one of chronic inflammation without any evidence of malignancy. Note the characteristic features: vesicle formation on the epidermal surface, interstitial edema, chronic inflammatory infiltration, parakeratosis and acanthosis (× 140).

and the intercellular bridges in the rete malpighii are preserved (fig. 5). Hyperkeratosis is frequently seen in Bowen's disease, while it is absent in "Paget's disease."

upward into the epidermis from the basal cell zone rather than down into the dermis. Here,

13. Montgomery, H.: Superficial Epitheliomatosis, Arch. Dermat. & Syph. **20**:339-357 (Sept.) 1929.

then, is an intraepidermal carcinoma which is primary, as opposed to the "Paget" type of change, which is secondary. In the former, all the characteristics of the primary carcinoma are present and intercellular bridges may be found.

3. *Simple Eczema.*—In simple eczema the microscopic changes in the epidermis are obperplasia, desquamation, edema and hydropic degeneration of epidermal cells.

One finds vesicle formation on the surface, parakeratosis (nucleation of cells in the exfoliative layer), acanthosis (thickening of the epidermis), interstitial edema and chronic inflammatory cell infiltration.

Fig. 7.—Intraepidermal metastatic carcinoma ("Paget's disease") resulting from extension by continuity of adenocarcinoma from underlying breast. Here one can see carcinoma cells arranged in strands filling interstices and lymphatics of the corium. At some points invasion through the basal layer into the epidermis can be seen, and in the layers of the epidermis are seen changes typical of "Paget's disease." These abnormal intraepidermal cells are identical in detail with the carcinoma cells found in the corium and the breast tissue (× 140).

viously not those of malignant processes (fig. 6). The basis of the process is inflammation, with secondary epidermal changes resulting from hy-

4. *Squamous Carcinoma.*—Of the 1,430 radical mastectomies performed at Barnard Hospital for carcinoma of the breast, in only 3 were there

Fig. 8.—Breast duct carcinoma extending to the nipple surface. Here one sees a typical ductal carcinoma. The carcinoma-filled duct is traced to the nipple in which there is encountered an ulceration and chronic inflammatory cell reaction. At the epidermal margin adjacent to the surface ulcer is found a typical secondary epidermal carcinoma ("Paget's disease") illustrated in figure 9. Thus is demonstrated metastasis to the epidermis from a breast carcinoma by extension along a duct (× 75).

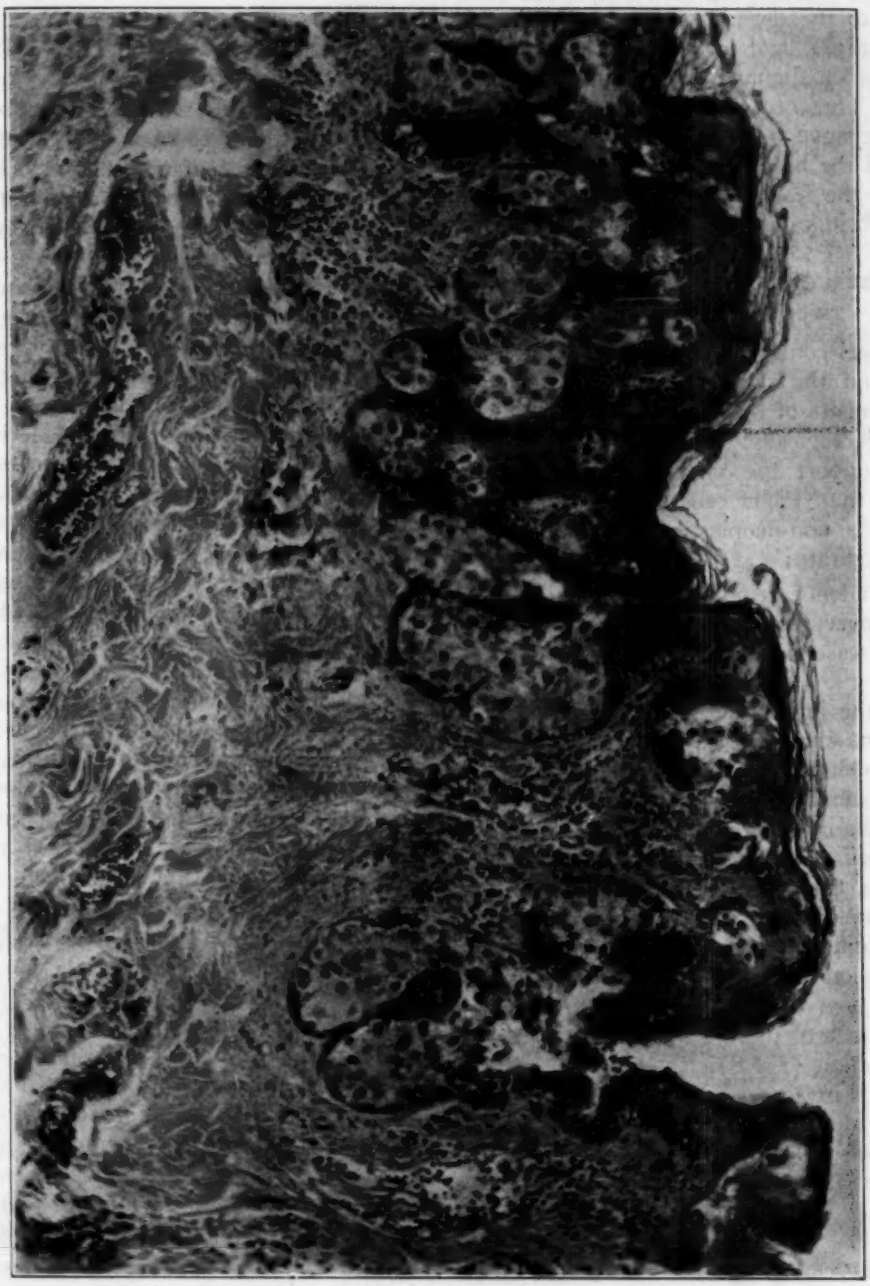

Fig. 9.—Secondary epidermal carcinoma ("Paget's disease") resulting from extension along a duct of a primary duct carcinoma of the breast. This section was taken from the margin of the ulcer seen in figure 8 and demonstrates the intraepidermal carcinoma cells identical with the duct carcinoma cells (× 150).

squamous cell carcinomas and 1 of these was in a man. In each instance the lesion was in the upper outer quadrant of the breast skin, well away from the region of the areola and nipple.

Squamous cell carcinoma presents little difficulty in differential diagnosis. The malignant invasion into the dermis of sheets of cells, the pearl formation and other characteristics of squamous cell malignancy are absent in "Paget's disease." The occasional case of "Paget's" cutaneous change associated with complete destruction of the basal layer may offer some difficulty, but the features of cell dissociation and absence of bridges prove the picture of "Paget's disease."

RESULTS IN A STUDY OF TWENTY-NINE CASES

The clinical course of these patients has been followed, and the skin and the glandular and stromal elements of the underlying breasts were studied pathologically. The findings in these 29 cases support the view of Jacobaeus and Muir, viz., the "Paget cell" is a malignant cell growing in a non-neoplastic epidermis. These cases demonstrate:

1. That adenocarcinoma of the breast was present in every case in which the diagnosis of "Paget's disease of the breast" was made histologically.

2. That the intraepidermal cell called "Paget cell" presents the identical histologic picture of the cancer cells found in the underlying carcinoma of the breast.

3. That the intraepidermal cancer cells extend into this locus in various manners. In some, continuity is traced from the breast carcinoma through lymphatics in the subcutaneous tissue and the corium (fig. 7); in others there is found direct extension along the interstices, and in still others one sees direct extension of malignant cells from ducts of the breast into the epidermis at their junction (fig. 8).

In some of my cases it has not been possible to demonstrate continuity of spread by any of these channels. However, I cannot but be of the opinion that it could be revealed in each case were adequate serial sections taken with this purpose in view.

4. That the changes in the skin of the breast also attest to this chain of events in their development. The intraepidermal clusters of cells sometimes present an acinar arrangement. The contiguous epidermal cells are usually distorted secondarily by compression or by hydropic degeneration, and in no instance do the epidermal cells present any gradation of changes ranging from normal to malignant. In no instance can intercellular bridges be demonstrated between the epidermal cells and the malignant cells, and in no instance does the epidermal cell show any tendency toward epidermal reproduction, such as might be expected in a primary epidermal malignancy.

NATURE OF THE MALIGNANT LESION OF THE BREAST

In this series of cases, there was nothing unusual in the type of breast cancer associated with the cutaneous manifestation. However, one interesting phenomenon was observed, which probably explains why the cutaneous lesion in some instances has existed for a long period before frank carcinoma of the breast could be recognized clinically. In some cases extremely early intraductal carcinoma was present, which had become quarantined by fibrous tissue before it became very large. This, plus its position immediately beneath the nipple, made it impossible to be palpated and limited its growth. It is this type of cancer that is more likely to go undiscovered by incomplete pathologic examination, and it is this same type that presents in a high frequency of cases no palpable mass. This intraductal type of carcinoma may be confused with benign lesions showng a pronounced degree of hyperplasia. However, on closer examination, one can discover areas at which the malignant cells have already broken through the elastica and have begun periductal infiltration. Just how long such a lesion may exist before it assumes this last characteristic, periductal invasion, is a matter of conjecture. Probably it varies. But in any event it is the most likely explanation for the existence of malignant cells in the epidermis for long intervals before frank carcinomatous masses appear in the breast proper. Apparently the malignant process in the duct may extend to the epidermis along the course of the duct and present a dermal and epidermal lesion long before actual invasion of an extensive nature occurs in other directions. On the other hand, there is adequate evidence that such an apparently trivial lesion may have metastasized at this early stage to the axillary lymphatics. It is for these reasons that the emphasis must be placed on early radical therapy irrespective of the presence of a palpable mass or of the duration of the cutaneous lesion. The fact that the cutaneous lesion has been present for a long period does not by any means preclude the fact that the patient also has microscopic evidence of cancer of the breast and even axillary metastases. Still, in the majority of the cases, a frank adenocarcinoma was present and it was impossible to ascertain

whether it originated in acinar or duct cells. In only 8 of the 29 cases in this series was there an intraductal carcinoma.

EXTRAMAMMARY "PAGET'S DISEASE"

In 1937 H. A. Weiner [14] reviewed the 57 cases which until that time had been reported as instances of "extramammary Paget's disease." He also presented the details of a case of his own. In his patient, he too was able to demonstrate that the intraepidermal cells were, in truth, neoplastic cells extending from a subjacent apocrine gland carcinoma of the vulva. Following a critical study, he concluded that only 15 of the 57 cases so reported entailed sufficient evidence (microscopic examination) to warrant such a diagnosis. In all the acceptable cases the changes occurred in the skin of the areas (axilla and anogenital regions) in which the apocrine sweat glands are present. Of these 15 cases, 9 presented definite evidence of carcinoma elsewhere than in the epidermis, and this in each instance was a glandular carcinoma. In the remaining 6 cases, either no mention was made of cancer or no adequate examination to discover its presence was performed. Others have reported intraepidermal metastatic carcinoma associated with epithelioma, melanoma and rectal carcinoma. Such an observation has led Drake and Whitfield and Civatte (cited by Weiner) to propose that "Paget's disease of the skin" is a nevocarcinoma.[15] Actually, however, a variety of tumors have produced the phenomenon, and it is unreasonable to postulate that all such metastases must be explained on the basis of one particular type.

COMMENT

From the evidence obtainable some tenable conclusions may be drawn:

1. Intraepidermal metastatic carcinoma has been repeatedly seen as an accompaniment of various types of malignant disease variously situated. Some of these metastases have been demonstrated as occurring by variable routes, viz., direct extension, ductal extension or by way of lymphatic channels.

2. The inaccuracy of explaining all such intraepidermal metastatic malignant growths on the basis of a single type of carcinoma is evident, since they may occur from underlying breast carcinoma, from epithelioma, from melanoma, from apocrine gland carcinoma and possibly from others.

3. Much of the difficulty which has arisen in regard to this picture is the result of eponymic labeling of the disease. While due credit should be attributed to Sir James Paget for first calling attention to the relationship between carcinoma of the breast and an eczema-like lesion of the nipple, the term "Paget's disease" has proved unfortunate because it has defeated the very purpose of illustrating this relationship. The placing of all such lesions into a group and labeling them "Paget's disease" has confused not only the clinician who desires to know what he is treating in order that he may treat it adequately but also the pathologist who attempts to theorize on the basis of 1 or several cases as to the nature of what he believes must be an entity, "Paget's disease."

One purpose back of the presentation of this study is to recommend that the terms "Paget's disease of the breast" and "extramammary Paget's disease" be abandoned altogether. The fact that the cells called "Paget cells" are carcinoma cells has been established. No typical and acceptable case of "Paget's disease" which has been adequately studied can be found that is not associated with carcinoma. It is essential to the welfare of such patients, then, that their maladies be recognized as cancer at the earliest possible stage, that is, when the cells are seen in the skin and not when the patient returns with obvious progression following inadequate treatment. When carcinoma cells are discovered in a benign epidermis, they should be called carcinoma cells rather than "Paget cells." In the case of breast lesions, the clinician could and should then treat the malady as a carcinoma primary in the breast, irrespective of palpable mass. In 41 per cent of 29 cases there was no palpable mass when the diagnosis of the skin was made, and yet adenocarcinoma of the breast was demonstrated microscopically. Thus, earlier recognition and earlier treatment of carcinoma in such cases will result.

14. Weiner, H. A.: Paget's Disease of the Skin and Its Relation to Carcinoma of the Apocrine Sweat Glands, Am. J. Cancer **31**:373-403 (Nov.) 1937.

15. The intraepidermal presence of *thèques* and clear cells in junction type nevi and in melanomas has been repeatedly observed. The clear cell of the junction nevus is easily differentiated from the "Paget cell." Opinion varies here, again, as to the nature of this intraepidermal cell, though from the evidence at hand it appears that the cell originates in the epidermal layer and does not represent an invasion into it. (Becker, S. W.: Cutaneous Melanoma: A Histologic Study, Especially Directed Toward the Study of Melanoblasts, Arch. Dermat. & Syph. **21**:818-835 [May] 1930. Nicolau, S.: Sur le phénomène de migration cellulaire intra-épidermique dans le névocarcinome, Ann. de dermat. et syph. **1**:746-762 [July] 1930. Traub, E., and Keil, H.: The "Common Mole," Arch. Dermat. & Syph. **41**:214-252 [Feb.] 1940.)

SUMMARY

1. "Paget cells" appear to be metastatic cancer cells.

2. In order to insure earlier recognition, refractory eczematoid lesions of the breast should be subjected to biopsy.

3. The origin of "Paget cells" may be from breast carcinoma, epithelioma, rectal adenocarcinoma, apocrine sweat gland carcinoma or other tumors.

4. The mode of extension may be by direct extension, retrograde lymphatic continuity or ductal spread.

5. Twenty-nine cases of "Paget's disease of the breast" are presented to attest to these facts.

6. In order to reduce confusion among pathologists and clinicians and in order to facilitate earlier and more rational therapy, the eponymic nomenclature ("Paget's disease of the breast" and "extramammary Paget's disease") should be abandoned.

7. "Secondary epidermal carcinoma" is suggested as a preferable term.

8. Treatment of secondary epidermal carcinoma must proceed along the lines of rational elimination of the primary carcinoma as well as of the cutaneous lesion.

9. In order to insure higher curability rate, treatment for secondary epidermal carcinoma of the breast must include radical mastectomy, whether the primary site can be palpably detected or not.

SKELETAL FIXATION OF MANDIBULAR FRACTURES

REPORT OF FIVE CASES, WITH NINE FRACTURES

HUGH D. BURKE, D.D.S.; DAVID L. MURPHY, M.D.
AND
W. A. McNICHOLS, M.D.
DIXON, ILL.

Injuries to the head have been steadily increasing in the past quarter of a century, and fractures of the mandible in particular have increased manyfold. The illustration (fig. 1) from Fomon's textbook [1] shows the various sites of fractures and the frequency of occurrence. While this is an accurate and standard chart, the present situation presents a more complex picture. The forces causing head injuries seem to be more intense, with the result that the fractures are frequently multiple and the displacement of the fragments extremely complicating.

Broken jaws have been recorded in medical history since 3,000 B. C., according to Breasted's [2] translation of the Edwin Smith surgical papyrus. Since this recording of such an injury, there have been numerous methods of treatment. We have tried many of these with varying degrees of success. Until the advent of skeletal fixation, there has not been a universal method of treatment adequate to handle any fracture that was presented. It is still possible for the condyle to be broken so short that pins cannot be inserted. In such a rare instance, an open operation would be mandatory.

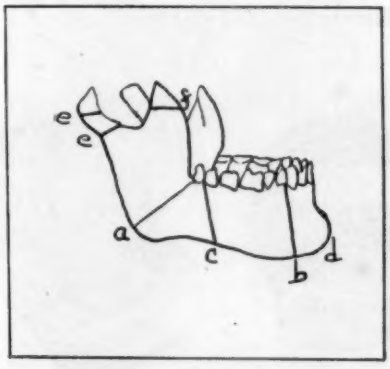

Fig. 1.—Sites of predilection of mandibular fractures, in order of frequency: (*a*) angle; (*b*) mental foramen; (*c*) molar region; (*d*) symphysis; (*e*) condyle and (*f*) coronoid process. (From Fomon.[1])

Because of the increasing frequency of injuries to the head with the resulting fractures of the mandible and the superior maxilla, we feel that each locality or each hospital should have a group which is interested in such fractures. The ideal team is an oral surgeon, an otolaryngologist and a general surgeon. The oral surgeon contributes his knowledge of the alinement of the teeth and the methods of securing a functioning bite. The otolaryngologist contributes his knowledge of the bones of the face and his ability to handle other fractures of the face as well as other complicating injuries of the head and neck. The general surgeon, with a large practice in fractures, advises as to the alinement of the teeth and the general condition of the patient.

Roger Anderson [3] has been credited with the practical development of the treatment of fractures by external appliance and pin fixation. This is the apparatus that we used. There are other appliances on the market, but we decided to use this because of its simplicity and light weight. It is simple, safe, comfortable and economical.

Gillies [4] listed the advantages of external skeletal fixation: 1. It is available for types of fractures which cannot be treated by other methods. 2. It may be immediately applied to any fracture. There is perfect control of all fragments and anatomic reposition. 3. It permits immediate movement of the temporomandibular joint. 4. It provides for cleanliness of the whole buccal cavity. We found all these advantages, and so far we have found no disadvantages.

We have seen roentgenograms of other patients, in whom the pins were placed too high.

1. Fomon, S.: Surgery of Injury and Plastic Repair, Baltimore, Williams & Wilkins Company, 1939, p. 1203.

2. Breasted, J. H.: Edwin Smith Surgical Papyrus, Published in Facsimile and Hieroglyphic Transliteration with Translation and Commentary, Chicago, University of Chicago Press, 1930.

3. Anderson, R.: Ambulatory Method of Treating Fractures of Shaft of Femur, Surg., Gynec. & Obst. **62**:865-873 (May) 1936.

4. Gillies, H. D.: Replacement and Control of Maxilla Facial Fracture, Brit. Dent. J. **71**:351-358 (Dec.) 1941.

They were in the loose tissue of the alveolar process and at various angles. If good results are to be obtained, the apparatus must be applied correctly. Waldron [5] has told how to place the pins:

The pins are inserted through the skin without incisions and through the mandible about 5 mm. above the lower border. The pins are placed at an angle of approximately 70 degrees and a hand drill is recommended for their insertion. The pin clamps are then applied and connected by a rod, and thus a strong and secure fixation of the fragment is assured. A second unit is placed in the adjacent fragment. The displacement is then reduced manually and the fracture immobilized by joining the two units by means of two universal fixation rod clamps and a fixation bar. This appliance can be loosened and adjustments made in the event complete reduction and proper alinement have not been secured at the time that it was first employed.

We are enthusiastic about this skeletal fixation. All of our pins have been well placed, and healing and occlusion have been excellent. We recommend wholeheartedly that before the first attempt at pinning condylar fragments one go to the laboratory. One should place the pins in the attached condyle and then make a window and observe where the pins are placed. Through a skin flap, the condyle on the opposite side should be severed from the mandible with a Gigli saw at the point of fracture in the patient to be operated on. Then after the skin flap has been replaced, the pins should be placed in this fragment. Thoma [6] used only one pin in the short fragment, but we prefer two. By placing two pins in the fragment, we have absolute fixation at once and the patient has all motions of his jaw.

All the patients in the following cases, with 1 exception, had their fractures reduced and skeletal fixation applied while they were under pentothal sodium anesthesia. The operating time, which included taking of roentgenograms for checking alinement, varied from forty minutes in the cases of angle fracture to three hours and forty minutes in case no. 5, with the multiple fractures.

REPORT OF CASES

CASE 1 (figs. 2 and 3).—A pullman porter, aged 63, was critically injured in a train wreck. Head injuries included a basal skull fracture and two fractures of the inferior maxilla, with the symphysis floating free and with pronounced displacement of the lower fragment. The patient was edentulous. His conditon was further complicated by severe burns on his neck extending to the lower border of the inferior maxilla. The burned area was infected; thus an open operation could not be considered. The general condition of the patient, which included additional fractures and burns, delayed the setting of the jaw two and a half weeks.

Owing to the callus formation, perfect alinement of the fragments was impossible. However, the end result was so good that dentures could be installed within three weeks after the immobilization of the fragments, at which time the patient could properly masticate solid food. Registration of the bite was obtained by McGrane's pin tracer technic. Immediately after the immobilization of the fragments with the skeletal fixation, the patient's mental haziness cleared. Food could be utilized, and the immediate improvement was evidenced in physical as well as mental well-being. The change effected in such a case is so pronounced that one must see it to appreciate it. The pins were removed at the end of eight weeks.

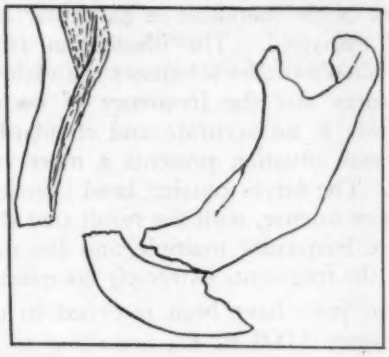

Fig. 2.—Diagrammatic drawing showing the symphysis floating free and overriding.

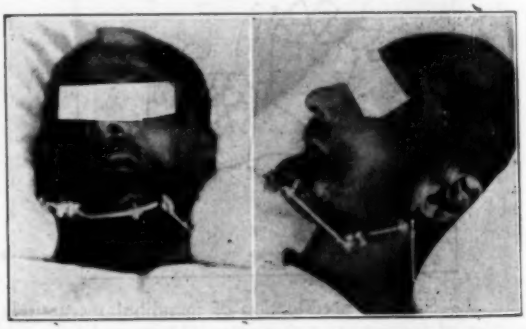

Fig. 3.—Firm and permanent fixation of the symphysis.

Cases 2 and 3 were instances of fracture of the angle of the jaw with the third molar loose and in the crevice of the fracture holding these ends apart. These angle fractures are the easiest of all to immobilize and aline with exterior fixation, but they present an unsolvable problem for any other method.

CASE 2.—A farmer was kicked by a horse. After suffering intensely for one week, he consented to have the fragments immobilized. Within three days he was consuming a regular diet, and in seven days he was

5. Waldron, C. W.: Skeletal Fixation in the Treatment of the Fractures of the Mandible, J. Oral Surg. **1**:59-83 (Jan.) 1943.

6. Thoma, K. H.: Fractures and Fracture Dislocation of the Mandibular Condyle, J. Oral Surg. **3**:3-59 (Jan.) 1945.

doing regular work on the farm. The pins were removed in the office at the end of eight weeks.

CASE 3 (figs. 4 and 5).—The patient was a man, aged 28. A roentgenogram showed a transverse fracture of the right mandible at the junction of the horizontal and the ascending ramus which transversed the entire width of the bone, splitting the alveolus of the wisdom tooth. There was a dislocation inward of the proximal fragment. The third molar in the crevice was extracted and four pins inserted, two horizontally and two vertically. This patient, as well as the preceding patient, had an excellent resultant bite.

Fig. 4.—Perfect alinement of an angle fracture.

Fig. 5.—Placement of pins in an angle fracture.

CASE 4.—A young woman, aged 28, was injured in an automobile accident. She had a shattering fracture of inferior mandible at the left mental foramen. She also suffered a crushing fracture of the left superior maxilla, with the left alveolar process pushed up to the left orbit. In addition, there were fractures of the right femur and both ankles. The patient was in a state of physical and mental prostration. Her mandible was fixed by skeletal fixation first. Her mental and physical condition cleared at once after the comfortable and permanent fixation of this painful fracture. Three days later the shattered fragments of the left superior maxilla were molded. The loss of the upper left central incisor, lateral incisor, cuspid, first bicuspid, second bicuspid and first molar greatly weakened the area. The second and third molars were brought into alinement and held in position by a Straith mouth piece. A screw was placed in the left inferior orbital ridge, and this was held out by a bar from a Straith head splint buried in plaster. After these fractures were fixed the other fractures were corrected. The superior maxilla fractures were healed in six weeks; the inferior mandible was held firmly in place for eight weeks. Roentgenograms then showed the fracture firmly healed and so the pins were removed. Prosthetic restoration was satisfactory both from the esthetic and the functional standpoint.

CASE 5 (figs. 6 and 7).—A girl, aged 18, was a passenger in a pleasure car which was in head-on collision. She suffered no injuries other than four fractures of

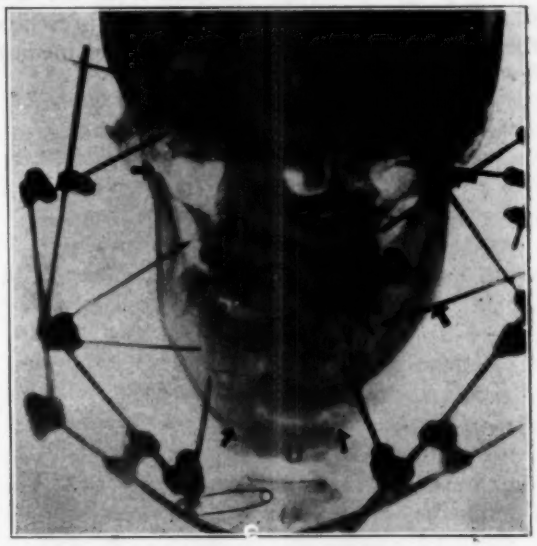

Fig. 6.—Four fractures of mandible, bilateral condylar, left angle, and symphysis crushed.

Fig. 7.—Close-up showing how pins were placed to hold all fragments. The plaster cap and supporting rod were used for ten days, as the masseter muscles were so bruised that the patient could not keep her mouth closed, and she complained of her throat becoming dry. In ten days this plaster cap was removed and all motions of the jaw were freely permitted.

the inferior mandible, the loss of the four lower incisors and the partial loss of her lower lip 0.5 inch (1.3 cm.) wide at the left angle of her mouth, tapering to an apex toward the right angle.

The fractures consisted of a shattering of the symphysis and a transverse fracture of the left angle at the junction of the horizontal and the ascending ramus whch transversed the entire width of the bone. Both condyles were broken off 5/8 inch (1.6 cm.) below the condylar process. The proximal fragments were both pushed to the right and the distal fragments were overriding to the left. Two pins were placed in the small stumps of the condylar processes. After that it was fairly easy to manipulate and fix the fractures. We had a great deal of trouble visualizing these fractures with roentgen ray. This girl's bite is not perfect, but it is functional. The pins were removed in ten weeks.

CONCLUSIONS

These cases were not selected from the files of a large hospital clinic. The patients presented themselves over a short period in the medical offices of a small community. They are cases which any physician or dentist may receive any day. Their importance lies in the fact that they illustrate the universal satisfaction which both physician and patient derive from this method of handling such difficult cases. The fractures can be reduced immediately; free movement is restored to the jaws; the whole process is clean and easily cared for, and the patient resumes normal activity in a minimum of time.

CORRECTION

In the article by Kenneth W. Penhale, D.D.S., M.D., entitled "Acrylic Resin as an Implant for Correction of Facial Deformities," in the May issue (ARCH. SURG. **50**:233, 1945) the reference in the first line of the legend for figure 8 should be to figure 7 instead of to figure 3.

PROGRESS IN ORTHOPEDIC SURGERY FOR 1944

A REVIEW PREPARED BY AN EDITORIAL BOARD OF THE AMERICAN ACADEMY OF ORTHOPAEDIC SURGEONS

VI. CONGENITAL DISLOCATION OF THE HIP

PREPARED BY A. BRUCE GILL, M.D., PHILADELPHIA

Turner [170] stresses the importance of early diagnosis and treatment of congenital dislocation of the hip. He feels that complications become worse with delay. The physical signs are listed as: I. Unilateral dislocation: (*a*) apparent shortening, (*b*) decrease in range of abduction, (*c*) piston motion, (*d*) asymmetry of skin folds about the thighs, (*e*) palpation of the head of the femur, (*f*) trochanter affected near the anterior superior spine. II. Bilateral dislocation: (*a*) wide perineum, (*b*) apparent lordosis, (*c*) unusually deep skin folds, (*d*) trochanters unusually near level of anterior superior spines, (*e*) palpation of femoral heads. It is noted in the roentgenograms that in congenital dislocation (1) the acetabular roof is sloping more than the normal 170 degrees, (2) the acetabulum is shallow, (3) the epiphysis is smaller, (4) the epiphysis is displaced, (5) Shenton's line is disturbed and (6) the metaphysial beak is displaced more laterally. The treatment should start as soon as possible. The complications are anteversion of the neck and aseptic necrosis.

Thompson [171] discusses primary acetabular dysplasia as the basic factor in congenital dislocation of the hip. The condition is hereditary and may be transmitted through either side of the family. This dysplasia may be recognized in the early weeks of life by the obliquity and the shallowness of the acetabulum as seen in roentgenograms of the hips. Dislocation may or may not occur, depending on the degree of the imperfection of the acetabulum, but if the dysplasia is not corrected during the period of growth the hip will always be abnormal, even though frank dislocation does not develop.

Natural growth processes will frequently overcome the dysplasia and cause a normal development of the acetabulum and of the head of the femur if the normal mechanics of the hip are restored and maintained. Early treatments to take advantage of normal growth from the beginning are imperative.

The author reviews the clinical and roentgenographic evidence of "predislocations" of the hip. [ED. NOTE.—I attach more importance to limitation of abduction than to asymmetry of the gluteal folds.] Predislocation should be treated by maintaining the hip in abduction and internal rotation until a roentgenogram shows that the hip has developed normally.

Dislocation should be reduced as soon as the diagnosis is made. Careful bloodless reduction is generally employed. If the dislocation cannot be reduced by manipulation or if reduction is not maintained, open reduction should be performed. Thompson has performed open reduction on a patient at as early an age as 5 months. He believes that the acetabulum develops more rapidly after open reduction than during fixation in a position of incomplete reduction. He advises osteotomy six weeks after open reduction, to correct anteversion of the neck. Fixation in plaster for six months after the open reduction is followed by unrestricted use of the extremity, without further orthopedic treatment. Periodic roentgenographic check-up is advocated thereafter until it is apparent that the hip joint has developed normally.

Lapin [172] discusses predislocation and describes 3 cases of suggestive physical signs of inequality of the two hip sockets, e. g., waddle gait, limp and asymmetry of buttock folds. In all the cases the roentgenologic examination shows normal conditions. A possible explanation offered is that on one side there may be a long capsular ligament or an intracapsular tissue of increased volume.

Michail [173] suggests that poor results in reduction are often due to difficulty of immobilizing

170. Turner, V. C.: Importance of Early Recognition of Congenital Dislocation of the Hip, M. J. Wisconsin **43**:613-617 (June) 1944.

171. Thompson, F. R.: Early Diagnosis and Early Treatment of Congenital Dislocation (Acetabulary Dysplasia) of the Hip, New York State J. Med. **44**: 1095-1102 (May 15) 1944.

172. Lapin, H.: Pseudocongenital Dislocations of the Hip in Infants: Three Cases, Arch. Pediat. **60**:649-652 (Dec.) 1943.

(Footnotes continued on next page)

the pelvis. He describes a pelvifixator, a steel plate with bars and straps devised by Nicod, which permits complete immobilization of the pelvis, with no interference with maneuvers, and causes no injury to the patient. Hitherto, to his knowledge no such apparatus has been described. A detailed illustrated description of the apparatus follows. Five cases are described in detail. Of 83 cases in which it was used, results were good in 23 and satisfactory in 29, and recurrences took place in 31. Results are much better in younger children than in older children. Nonsurgical treatment is the method of choice, even for older children. If poor results are noted, surgical treatment should be instituted at about 5 years of age. For an irreducible congenital dislocation, osteotomy may be used.

Ponseti [174] made a study of 129 patients (one hundred and seventy-three hips treated) in the clinic of Dr. Arthur Steindler at the State University of Iowa College of Medicine to determine the factors which prevent normal development of the hip during the course of treatment for congenital dislocation of the hip. All patients were under observation for more than four years.

The author divides his cases into three groups: (1) cases of prenatal dislocations, present at birth; (2) cases of postnatal dislocations, presenting predislocation at birth and progressing to complete dislocation, and (3) doubtful cases, seen after infancy, presenting both a primary and a secondary acetabulum, with the time of dislocation unknown.

Treatment of the first type is usually unavailing. The structures of the hip are too far removed from the normal.

Predislocation, discovered in the early weeks or months of life, is treated by some method of abduction. Almost uniformly good results are obtained in these cases. The head of the femur is maintained securely in the acetabulum, and normal growth of the acetabular roof takes place during this early period.

Complete postnatal dislocation should be reduced by gentle manipulation. The hip is then fixed in plaster in a position of 90 degrees of flexion and 60 to 70 degrees of abduction (Waldenström position) for a period of three to four months. Then, with the patient under anesthesia, the legs are placed in the Lange position with internal rotation and retained in plaster for another two months. The author then maintains abduction by a bar between the feet. The bar is attached to plates on the shoes. A pin is put into the plate to limit outward rotation at 75 degrees and to permit free inward rotation. Movement of the hips is permitted by this apparatus. The appliance is kept on for from two to six months, depending on the development of the acetabulum. Walking is then permitted for two hours daily for the next month, and the time is gradually increased.

If bloodless reduction cannot be accomplished, open reduction is advised.

The author believes that failure to secure a successful result is due to (1) epiphysitis of the head, (2) tendency of the head to become subluxated when the child begins to walk and (3) osteosclerosis of the acetabular roof.

Leveuf [175] has noted that in congenitally dislocated hips reduced by orthopedic methods one may often find a deformity of the upper end of the femur, especially at the level of the head. Of 600 cases studied roentgenologically for late results, only 25 per cent showed good anatomic and functional results. In more than half of the remaining 75 per cent there was a deformity of the head of the femur. Various theories of pathogenesis are reviewed. In reports of 12 biopsies of cartilage of the head removed at operative reduction, the histologic changes are described, including cavitation and ulceration. Nine specimens were from children of 2 to 5 years, and orthopedic treatment had been initiated at 8 or 10 to 14 months in 4 cases, at 22 months in 2 cases and at 30 months in 3 cases. All the patients showed pronounced lesions of the cartilage of the head of the femur, with changes similar to those seen in arthritis deformans. These observations show that orthopedic maneuvers for reduction may lead to severe and permanent lesions of the hip joint. Orthopedic reduction should always be attempted in cases of congenital dislocation of the hip, but under control of arthrography, which reveals any obstacles to reduction which would require surgical removal. This method avoids prolonged immobilization in a faulty position. In cases without cartilaginous lesions, the results were excellent. Perfect function can be hoped for in cases in which the joint has not been destroyed by futile orthopedic manipulation.

Nathanson and Lewitan [176] report 3 cases showing the association of spina bifida and dis-

173. Michaïl, J.: Treatment of Congenital Dislocations of the Hip in Children, Praxis **32**:695-700 (Sept. 30) 1943.

174. Ponseti, I.: Causes of Failure in Treatment of Congenital Dislocation of the Hip (Improved Method, Including Use of Abduction Bar), J. Bone & Joint Surg. **26**:775-792 (Oct.) 1944.

175. Leveuf, J.: Pathology of Grave Lesions of Head of Femur Following Unsuccessful Attempt at Orthopaedic Reduction of Congenital Luxations of Hip, Mém. Acad. de chir. **68**:400-403 (Nov. 11-18) 1942.

location of the hips. The authors believe that the dislocations are the result of the neural defect produced by the spina bifida. They point out that in severe forms it is accompanied with other anomalies: anencephaly, hydrocephalus, talipes equinus and others. The abnormality most commonly occurs in the lumbosacral region, and the neurologic signs manifest themselves in the lower limbs. Often one group of muscles show fair power, whereas antagonists may show complete paralysis. This was the condition in the 3 cases presented. Urinary incontinence and, less frequently, fecal incontinence are present. Two types of dislocation are distinguished: (1) the endogenous, in which there is a developmental arrest in the acetabular roof, and (2) the dynamic, in which abnormal forces are present, e. g., relaxation of the hip ligaments and imbalance of the muscle. The dislocation usually occurs in the absence of power of the abductor and external rotator muscles. In the latter cases, maldevelopment of the acetabulum due to disuse follows.

Roberts [177] emphasizes the necessity of constructing the shelf or buttress above the head of the femur in such a manner that the new portion of the acetabulum is molded on top of the head and continues the arc of the circle which is present in the original acetabulum. [ED. NOTE.—It is often necessary to revise the arc of an oblique acetabulum by reflecting the roof downward.] He describes the method of open reduction and of closing the capsule with sutures so that the capsule overlaps the margin of the newly constructed shelf. He employs a bone strut to fix the iliac bone flap in firm contact with the head.

176. Nathanson, L., and Lewitan, A.: Spina Bifida Associated with Dislocation of the Hip, Am. J. Roentgenol. **51**:635-638 (May) 1944.

177. Roberts, F. B.: Plastic Shelf Operation for Dislocations of the Hip, Ohio State M. J. **40**:650-656 (July) 1944.

VII. TUBERCULOSIS OF BONES AND JOINTS

PREPARED BY ALAN DE FOREST SMITH, M.D., AND STAFF OF THE NEW YORK ORTHOPAEDIC DISPENSARY AND HOSPITAL, NEW YORK

During 1944 there were comparatively few articles on the subject of tuberculosis of bones and joints of sufficient interest to include in a review of progress. However, it is encouraging to note an increase in experimental studies toward developing inhibiting or bacteriostatic agents that may be effective against tuberculosis. The effect of a number of sulfonamide compounds, including Diasone and promin, has been studied by a number of investigators, both in the laboratory and on human patients. The results appear to justify the hope that some important result may be expected, although the subject still is in the experimental stage.

In a study by Petter and Prenzlau,[178] Diasone (disodium formaldehyde sulfoxylate diaminodiphenyl sulfone) was therapeutically administered to 78 tuberculous patients for periods ranging from sixty to two hundred and seventy-five days. Seventy-two of the patients had pulmonary lesions, 5 had lesions of bones and joints and 1 had genitourinary lesions. The drug was given orally to all patients and applied locally as well to empyema cavities and abscesses about joints. The dose was usually 0.33 Gm. with meals (1 Gm. per day). Toleration was improved if the drug was started at 0.33 Gm. per day for three days, increased to 0.66 Gm. for the next three to five days and then raised to the standard dose of 1 Gm. per day. Enteric-coated capsules gave less gastric disturbance. Evidences of toxicity were headache, gastric upset, palpitation, malaise, occasional visual disturbances and "blue skin." Also noted in some patients were an increase in temperature and an increase in cough and expectoration at the onset of treatment. None of these reactions were alarming in severity, none were unbearable and none irreversible. In 3.7 per cent of the cases, the drug was stopped because the patients preferred not to experience the unpleasantness of reactions. Studies of the blood showed an average initial drop from 4,700,000 red cells and 12.5 Gm. of hemoglobin to 2,700,000 red cells and 8.8 Gm. of hemoglobin in the third and fourth weeks and then a gradual rise to about 4,000,000 red cells and 10.3 to 11 Gm. of hemoglobin. Depression of the total leukocyte count did not occur, and neutropenia was not observed. Evidences of damage to the kidneys or liver were not observed clinically or by histologic study in 4 cases coming to autopsy after twelve to seventy-two days of full doses of the drug. With administration of 1 Gm. of Diasone daily, blood levels were maintained between 1.5 and 2 mg. per hundred cubic centimeters. In a small group of cases, the concentration of "free" Diasone in the blood ranged from 1.7 to 2.5 mg., in the cerebrospinal fluid

178. Petter, C. K., and Prenzlau, W. S.: Observation on Clinical Application of Diasone in Human Tuberculosis (Eight Month Study), Illinois M. J. **85**: 188-197 (April) 1944.

from 1.5 to 2 mg., in the urine from 44 to 80 mg. and in the bronchial secretion from 0.5 to 1 mg. per hundred cubic centimeters.

As the patients acquired a tolerance to the compound, general well-being improved and body weight remained at pretreatment level or increased. Cough and expectoration, in the presence of more acute lesions, increased at first and then gradually subsided. Conversion of sputum from positive for tubercle bacilli to negative occurred in 62 per cent of the patients treated from sixty to one hundred and twenty days. As observed by roentgen ray examination, clearing of parenchymal infiltration occurred in 75 per cent of patients, and there was also some increase in fibrosis. These changes for the most part began to take place at from thirty to sixty days. Closure of the cavity, or at least disappearance of cavity outlines, occurred in 37.5 per cent of 40 patients. In 34 patients, the blood sedimentation rate dropped from an average initial value of 45 mm. per hour (Westergren) to 10 mm. per hour after twenty-four weeks of therapy. Although most patients were bed patients and rest was probably a factor, similar favorable changes occurred also in patients who were ambulant and in others who continued to work full time. Four per cent of the patients, in whom the tuberculosis was far advanced, died after treatment for sixty days or longer; 6 per cent of the patients were considered worse, and in 3 per cent there was no apparent change. Improvement was recorded in 100 per cent of the patients with minimal disease, 90 per cent of those with moderately advanced disease and 76 per cent of those in far advanced stages. Improvement was recorded as slight in 22 per cent, moderate in 35 per cent and pronounced in 30 per cent. There were 5 patients with tuberculosis of bones and joints. One, with tuberculosis of a hip joint, was made worse, 2 were moderately improved and 2 were greatly improved. The authors conclude that Diasone, though not ideal, is an advance toward the goal of chemotherapy for tuberculosis and that it produced favorable changes in the majority of their patients in shorter time and of greater degree than would reasonably be expected on the regimen employed without the compound.

Feldman and Hinshaw [179] found that in experimentally induced tuberculosis in guinea pigs a daily dose of 200 to 250 mg. of Promizole had a therapeutic efficacy comparable to a daily dose of 400 to 500 mg. of Promin (p,p′-diaminodiphenylsulfone-N,N′-didextrose sulfonate) and exerted a favorable influence even though treatment was not started until six weeks, ten weeks or fourteen weeks after animals had been inoculated with tubercle bacilli.

Feldman and Hinshaw [180] report experiments which indicate that 4,4′-diaminodiphenylsulfone is an effective agent in inhibiting or combating experimental tuberculosis in guinea pigs. Continuous prolonged administration yields cumulative benefits not attained in short term experiments. In the long term experiment, extending to two hundred and twenty-eight days, 71.4 per cent of the untreated animals died, while in the treated group only 28.6 per cent died. Histologic studies showed that the animals which had received the drug either were without demonstrable lesions or had residual foci in which the process was arrested, calcified or healed. Although producing some anemia, the drug was not excessively toxic for guinea pigs in the dose used. Efforts to modify 4,4′-diaminodiphenylsulfone to obtain a compound more suitable for clinical application should be encouraged, since the possibilities seem many.

Armstrong, Raie, Lucas and Greey [181] observed that Promin, used under the strictly defined experimental conditions of Feldman, Hinshaw and Moses, influenced favorably the course of experimental tuberculosis in guinea pigs. If, instead of the standard oral dose of 300 mg. per day for nine and ten months, 400 or 500 mg. per day was given for three to six weeks to animals which were perhaps more heavily infected, no therapeutic effect was noted.

According to Feldman, Hinshaw and Mann,[182] promizole (4,2′-diaminophenyl-5′-thiazolylsulfone) exerted a deterrent effect on previously established experimental tuberculosis in guinea pigs that was only slightly inferior to that of Promin. It produced moderate blood dyscrasia and goiter, but these effects were reversible. The low toxicity of Promizole for human beings and the tuberculochemotherapeutic properties of the drug in experimentally infected guinea pigs appear to justify its clinical trial.

179. Feldman, W. H.; Hinshaw, H. C., and Mann, F. C.: Effects on Experimental Tuberculosis of 4,2′-Diaminophenyl-5′-Thiazolesulfone (Promizole): Preliminary Report, Proc. Staff Meet., Mayo Clin. **19**:25-33 (Jan. 26) 1944.

180. Feldman, W. H.; Hinshaw, H. C., and Moses, H. E.: Effects on Experimental Tuberculosis of 4,4′-Diaminodiphenylsulfone, Am. J. M. Sc. **207**:290-305 (March) 1944.

181. Armstrong, A. R.; Raie, M. V.; Lucas, C. C., and Greey, P. H.: Effect of Promin on Experimental Tuberculosis, Am. Rev. Tuberc. **50**:160-162 (Aug.) 1944.

182. Feldman, W. H.; Hinshaw, H. C., and Mann, F. C.: Promizole in Tuberculosis: Effect on Previously Established Tuberculosis of Guinea Pigs of 4,2′-Diaminophenyl-5′-Thiazolysulfone (Promizole), Am. Rev. Tuberc. **50**:418-440 (Nov.) 1944.

Freedlander,[183] in a brief review, states that he has tested some ninety derivatives of benzophenone for their tuberculostatic effect in vitro. Benzophenone is low in toxicity and shows moderately high bacteriostatic action. The following derivatives increased the bacteriostatic action: -4-chloro; 2-chloro; 2,4′ dichloro; 2-iodo; 4-methyl; 4-methoxy; 4-ethoxy, and thiobenzophenone. It was not possible to find a definite chemical pattern in the relationship between chemical structure and tuberculostatic action, but an optimal lipid-water solubility ratio was discernible.

Petter[184] published a note to bridge the gap between "news stories" and the appearance of proposed reports in medical literature. Diasone has been used in treatment of 139 patients. It is still an experimental therapeutic agent. Much more must be learned about dosage, toxic reaction, change which takes place in the tuberculous lesions and many other ramifications of such a problem. One cannot be too emphatic at this time in stating that this compound is not ready for even limited distribution until a great amount of investigational work is completed.

Buu-Hoï and Ratsimamanga[185] reported that dihydrochaulmugryl cinnamate in ethyl dihydrochaulmugrate administered to tuberculous guinea pigs resulted during the seventy-eight day period of the experiment in slower development of tuberculosis, a lowered mortality (30 per cent, as compared with 83 per cent in controls) and anatomically more discrete lesions as compared with those of control animals. In tuberculous guinea pigs on a diet low in ascorbic acid, the evolution of tuberculosis is more rapid than that in animals on a diet high in ascorbic acid.

Feldman and Moses[186] reported experiments in which diphtheria toxoid failed to exert any significant deterrent effect on tuberculosis experimentally induced in guinea pigs and rabbits.

Callomon and Groskin,[187] using promin, disodium formaldehyde sulfoxalate diaminodiphenylsulfone (compound 2398) and 4(α-pyridil-N-sulfonamide) phenyl 2-azo-8-amino-1-naphthol 5,7-disulfonic acid (compound 2816), produced evident inhibition of the development of experimental tuberculosis in guinea pigs observed over a period of six weeks. Sulfanilamide, sulfapyridine, sulfathiazole and sulfathiazoline showed no appreciable effect under the same conditions of experimentation. Judged from mortality and histologic change, Promin produced the most beneficial results.

Penicillin, penatin and extracts of Raulin-Thom culture mediums of Penicillium notatum and Penicillium cyclopium were examined by Smith and Emmart[188] for their bacteriostatic action against tubercle bacillus in vitro, for their inhibiting action of tubercle formation on chorioallantoic membrane of the chick embryo and for their chemotherapeutic effectiveness against experimental guinea pig tuberculosis. Extracts of the culture medium of P. notatum gave good but variable inhibition of growth of tubercle bacilli in glycerin bouillon. All the preparations tested appeared to have some activity in reducing the extent of tubercle formation on the chorioallantoic membranes but did not decrease the incidence of infection. Penicillin exhibited no effect on experimental tuberculosis in the guinea pig; a slightly favorable effect was obtained with extracts of the culture mediums of P. notatum. At best, the chemotherapeutic activity of these preparations was slight compared with some of the sulfones previously investigated by the authors.

Schwartz[189] studied 4 rabbits given subarachnoid-suboccipital injections of tubercle bacilli. Meningitis, meningomyelitis, radiculitis, ganglionitis and tuberculoma developed. Following a review of the literature on experimental spinal tuberculosis, the author stresses the fact that in man the least frequent localization of tuberculoma is in the spinal cord. For the development of tuberculoma, not only the duration of the infection but probably the type and the dose of bacilli play a part. In most of the rabbits, paresis, paralysis and muscular atrophy developed. This is explained by the greater infiltration at the level of the cauda equina, which regulates motor sensibility and trophism of the hindlegs. This localization also favors limitation of the infection.

Hinshaw, Feldman and Pfuetze[190] studied evidence based on the administration of pro-

183. Freedlander, B. L.: Experiments in the Chemotherapy of Tuberculosis, California & West. Med. **61**: 85 (Aug.) 1944.

184. Petter, C. K.: Diasone in Tuberculosis, J. A. M. A. **124**:385 (Feb. 5) 1944.

185. Buu-Hoï and Ratsimamanga, A. R.: Ethyl Dehydrochaulmoograte Combined with Cinnamic Acid Derivatives in Experimental Tuberculosis, Compt. rend. Soc. de biol. **136**:772-774, 1942.

186. Feldman, W. H., and Moses, H. E.: Effect of Diphtheria Toxoid on Experimental Tuberculosis, Internat. J. Leprosy **11**:36-42 (Dec.) 1943.

187. Callomon, F. F. T., and Groskin, L.: Therapeutic Effect of Some New Derivatives of di-Amino-di-Phenylsulfone in Experimental Tuberculosis of Guinea Pigs, Tuberculology **7**:21-25 (Feb.) 1944.

188. Smith, M. I., and Emmart, E. W.: Action of Penicillium Extracts in Experimental Tuberculosis, Pub. Health Rep. **59**:417-423 (March 31) 1944.

189. Schwartz, L.: Experimental Tuberculosis, Día méd. **16**:204-206 (March) 1944.

(Footnotes continued on next page)

mizole to 56 patients which indicated that this drug is unique among numerous compounds of this class studied in being easily administered, well absorbed and of extremely low toxicity for human beings. Evaluation of clinical results was not possible at this early period of the study.

Steenken, Heise and Wolinsky [191] state that promin when fed by mouth exerts a definite retarding effect on experimental tuberculosis in guinea pigs and that vaccination with attenuated living tubercle bacilli combined with treatment with Promin induces a greater inhibition on the progress of the disease than treatment with Promin in the unvaccinated animals.

Auerbach and Stemmerman [192] present a study of 132 patients with pathologically proved tuberculosis of the spine, of whom 100 had roentgen ray examination within six months prior to death. The area involved was one vertebra in 6 cases (4 per cent), two vertebrae in 39 (30 per cent), three vertebrae in 24 (18 per cent) and multiple lesions in 63 (48 per cent). The area of spine involved was typically the dorsal portion, the lumbar portion, the sacrum and the lower and upper cervical portions, in that order. The disease develops in the vertebral body, and the intervertebral disk is involved by extrusion. Two types of pathologic lesion are described: 1. The productive type (sclerotic) shows bone of a yellow color which is firm and maintains its morphologic integrity; the disk remains intact, and the marrow spaces are filled with tuberculous granulation tissue which erodes but does not destroy trabeculae. 2. The exudative (caseous, destructive) type shows yellow bone with areas of liquefaction which may contain sequestrums; the bony architecture is completely destroyed by areas of caseation with extrusion to the disk, compression of the body and gibbus formation. Sixty-three per cent of destructive lesions were correctly diagnosed roentgenologically. Of 30 cases of productive lesions, none were diagnosed correctly.

After a comparison of postmortem roentgenograms with antemortem roentgenograms, it was felt that in some cases with a definite history of a primary focus diagnosis might be made by an apparent sclerosis shown by roentgenogram. This sclerosis is thought to be caused by the productive changes seen in pathologic examination.

A case of a large cold abscess dissecting along the psoas, of ten months' duration, is discussed. The diagnosis of abscess was easily made. Roentgenograms consistently showed nothing abnormal, yet at autopsy nearly every vertebra was diseased, some partially but the majority completely.

When other roentgenologic evidence of vertebral tuberculosis is present, the possibility of the productive (sclerotic) type of disease should be considered. It is suggested that serial roentgenograms might be helpful in demonstrating changes in osseous density as the productive lesion progresses. Even when destructive lesions are typically present, the rest of the spine should be carefully scrutinized for evidence of possible productive disease. Evidence of "cold abscess" only is sufficient reason for careful roentgenologic studies of the spine for tuberculosis, although all other signs may be absent.

[ED. NOTE.—This study supplements an earlier one by Cleveland and Bosworth, in which the frequent occurrence of areas of necrotic sclerotic bone in tuberculosis of the spine was pointed out. These authors ascribed such lesions to ischemia caused by stripping of the periosteum by the abscess.]

Gill [193] presents the thesis that the pronounced shortening of the entire lower extremity sometimes seen in cases of tuberculosis of the hip is due not to disease but to premature closure of the epiphysial cartilages of the femur or tibia or of both. He presents the histories of 15 cases of tuberculosis of the hip in which this complication occurred. In every case the onset of the disease was before the seventh year of age. The damage to the cartilaginous plate occurred not from any disease process but from pronounced decalcification of the bones and alteration in the cartilage, making it more susceptible to trauma. In 3 cases there was a diaphysial fracture causing closure of the epiphysial plates of both femur and tibia.

In order to prevent the occurrence of this complication, the avoidance of long periods of immobilization in plaster is advised whenever possible. It is suggested that the femur and the tibia be measured every six months in children with tuberculosis of the joints. If it is found that one of the epiphysial cartilages has closed prematurely, an estimate of the final result in the

190. Hinshaw, H. C.; Feldman, W. H., and Pfuetze, K. H.: Clinical Administration of 4,2'-Diaminophenyl-5'-Thiazolesulfone (Promizole) in Tuberculosis: Preliminary Report, Proc. Staff Meet., Mayo Clin. **19**: 33-36 (Jan. 26) 1944.

191. Steenken, W., Jr.; Heise, F. H., and Wolinsky, E.: Treatment of Experimental Tuberculosis in Vaccinated and Non-Vaccinated Guinea Pigs with Promin, Am. Rev. Tuberc. **48**:453-460 (Dec.) 1943.

192. Auerbach, O., and Stemmerman, M. G.: Roentgen Interpretation of Pathology in Pott's Disease, Am. J. Roentgenol. **52**:57-63 (July) 1944.

193. Gill, G. G.: The Cause of Discrepancy in Length of the Limbs Following Tuberculosis of the Hip in Children, J. Bone & Joint Surg. **26**:272-281 (April) 1944.

length of the extremity should be made and an epiphysial arrest should be done in the opposite extremity at the appropriate time.

Mordasini [194] discusses the planogram as a valuable addition to the conventional roentgenograms in the diagnosis of tuberculosis in bone. A positive diagnosis can be made earlier. This technic is more useful in the frontal than in the lateral planes in tuberculosis of the spine. Case reports show that the early spinal lesion is not in the anterior part of the vertebra but that it starts in the central or the posterior portion of the body of the vertebra. Narrowing of the intervertebral spaces appears later.

[ED. NOTE.—The laminagraph has been proved to be of value in the detection of areas of tuberculosis of the vertebrae at the New York Orthopaedic Dispensary and Hospital.]

Meng and Wu [195] reviewed 70 cases of tuberculosis of flat bones of the vault, 40 of which had sufficient data for a definite diagnosis. Of the 40 cases, 20 were proved histologically and 5 by guinea pig inoculation or culture; 15 had sufficient clinical signs to justify the diagnosis. Eighty per cent of the patients were under 20 years of age. There were 23 men and 17 women. Trauma was not important or essential but may have been contributory. Eighty-five per cent had associated tuberculous lesions, and 50 per cent had pulmonary tuberculosis. Most lesions were, therefore, secondary hematogenous lesions starting in the diploe, and the tables were involved by extrusion. Two types of lesion are recognized: (*a*) the circumscribed (perforating) type of Volkmann (38 cases) and (*b*) the diffuse (infiltrating) type of Koenig (2 cases). There was a single lesion of the skull in 23 cases and multiple lesions in 17 cases. Most frequently involved were the frontal and the parietal bones because they contain a greater amount of cancellous bone. The onset was insidious, with only swelling evident. Pulsation of the mass indicates perforation of both tables. Differential diagnosis includes lipoma, sebaceous cyst, syphilis and tumor. Results of roentgenologic examination are not typical and show only a round or oval single or a multiple punched-out defect. Aspiration is helpful. Treatment should be complete excision without drainage in the absence of a sinus, and the dura should be let alone. High voltage roentgen rays are sometimes of benefit.

Some of the causes of painful shoulder with radiation of the pain into the arm are discussed by Cohn.[196] No attempt is made to classify all the conditions which cause painful shoulder, but the diseases mentioned, with illustrative cases, are as follows: hypertrophic arthritis of the cervical portion of the spine, carcinoma metastasis to the cervical portion of the spine, herniated cervical intervertebral disk and tuberculosis of the cervical portion of the spine. The author also directs attention to these conditions which may be responsible for pain in the shoulder, i. e., cervical rib, the various neuritides and local lesions of the shoulder region, including arthritis, periarthritis, bursitis and tears of the supraspinatus tendon. A careful and detailed physical and roentgenographic examination is stressed as a necessary means of securing an accurate diagnosis.

The author observes that referred pain in tuberculosis of bones and joints is a common symptom, and any complaint referable to the shoulder, especially in the absence of definite physical abnormalities, should make one suspicious of a lesion of the cervical portion of the spine. Roentgenographic studies of the cervical portion of the spine should always be made in cases in which pain in the shoulder is the symptom, especially when local signs are absent, because not infrequently advanced changes will be noted on the roentgenogram even when the patient does not complain of symptoms referable to the neck. The author believes that the modus operandi of the referred pain in many cases of tuberculosis of the cervical portion of the spine is due to compression of the nerve roots by tuberculous granulation tissue. The referred pain, as a rule, promptly responds to immobilization of the cervical portion of the spine in a plaster cast.

194. Mordasini, E.: Beitrag zur Tomographie der Knochen und Gelenke unter besonderer Berücksichtigung der Knochen und Gelenktuberkulose, Schweiz. med. Wchnschr. **74**:123 (Feb. 5) 1944.

195. Meng, C. M., and Wu, Y. K.: Tuberculosis of the Flat Bones of the Vault: Forty Cases, Chinese M. J. **61**:155-171 (April-June) 1943.

196. Cohn, B. N. E.: Painful Shoulder Due to Lesions of Cervical Spine, Am. J. Surg. **66**:269-274 (Nov.) 1944.

VIII. CHRONIC ARTHRITIS

PREPARED BY JOHN G. KUHNS, M.D., BOSTON

The appearance of arthritis and rheumatic fever in the armed forces has spurred further investigation and the development of special services for their treatment. The newer antibiotic substances have been carefully studied in attempts to prevent or relieve these diseases.

Most of the papers appearing during the year are concerned with some special symptom or special type of treatment. In a general paper, Wright [197] describes the importance of arthritis as a disabling disease. He states that it is ten times as common as tuberculosis or diabetes and seven times as common as cancer. In England chronic arthritis causes one sixth of the industrial disability and accounts for one tenth of the money for pensionable invalidity. He advocates the establishment of special clinics with trained personnel and proper facilities for physical therapy. He compares the problem to public health with that of tuberculosis.

A number of papers discuss possible etiologic factors. The problem of allergy in relation to sensitivity to food in the development of arthritis as it appeared in 10 personally observed cases is discussed by Turnbull.[198] In the patients the arthritic symptoms disappeared when the foods to which they were sensitive were eliminated. To determine the sensitivity, repeated tests are necessary. Selye and his co-workers [199] believe that the adrenal cortex can play an important role in the pathogenesis of rheumatic and rheumatoid conditions in man. In laboratory animals, administration of desoxycorticosterone acetate in large doses caused nephrosclerosis, Aschoff bodies in the heart and periarteritis nodosa. Arthritis was found in a few animals. Arthritis was found with much greater frequency if thyroidectomy had been performed on the animals or if the adrenal glands had been removed, especially if the animals had been kept in cold surroundings. In such instances, arthritis was found in fourteen days. This arthritis resembled that found in rheumatic fever. Gauss [200] calls attention to the frequently observed relationship between disturbances in the biliary system and rheumatoid arthritis. Correction of disturbances in the biliary system often leads to relief of the arthritis. The author considers two possibilities. The gallbladder may be a focus of infection, or biliary disturbances may lead to metabolic faults. Jaundice often relieves arthritis temporarily. The relationship is obscure.

[Ed. Note.—In the development of the so-called prodromas of arthritis, a great number of things have been suspected. Probably any prolonged physiologic disturbance can be a precursor of symptoms of arthritis, but whether rheumatoid arthritis is initiated by an infection, as I understand the term, is still uncertain.]

Lyford and colleagues [201] have observed 3 cases of polyarticular arthritis as a complication of granuloma inguinale. In 1 patient, there were ulceration in many of the joints and necrosis of bone. In another, there was involvement of two vertebrae and a hip joint. The third patient had lesions in the bones of the hand and forearm, but there were no joints involved. All the patients had fever and persistent anemia, but there were no sequestrums and no pus. Donovan bodies were found in articular tissues. Ropes [202] states that atypical, asymmetric or monarticular arthritis was frequently seen in the early stages of rheumatoid arthritis. For such patients, diagnosis was difficult. For patients presenting atypical symptoms, adequate treatment with prolonged rest in bed could hasten remission and might prevent progression. Hench and Fox and Gilbert [203] studied the articular complications seen in 266 patients with epidemic cerebrospinal (meningococcic) meningitis. Three types of arthritis were seen: (1) symmetric polyarthritis of short duration and not severe seen in the first few days of the disease; in such cases there might be periarticular and intra-articular hemorrhage; (2) an articular effusion of varying degree coming on after the fifth day; in this type, infection seemed to be present and articular damage might follow, and (3) arthropathies associated with serum sickness; there was a serous effusion into the joint, of short duration and with a favorable prognosis. Arthritis was observed in 10 patients: in 4 of 215 patients observed in the ten years before chemotherapy was used and in 6 of 51 patients observed in the two years since sulfonamide compounds were used. The lessened mortality, the authors believe, had permitted the greater appearance of complications. Hench and Rosenberg [204] describe a type of disease of joints which they call palindromic rheumatism. There are repeated attacks of articular inflammation, with no lasting

197. Wright, H. P.: The Challenge of Arthritis, Canad. M. A. J. **51**:264-265 (Sept.) 1944.

198. Turnbull, J. A.: Changes in Sensitivity to Allergic Foods in Arthritis, Am. J. Digest. Dis. **11**:182-190 (June) 1944.

199. Selye, H.; Sylvester, O.; Hall, C. E., and Leblond, C. P.: Hormonal Production of Arthritis, J. A. M. A. **124**:201-207 (Jan. 22) 1944.

200. Gauss, H.: Review of Role of the Biliary System in Arthritis, Am. J. Digest. Dis. **11**:271-276 (Sept.) 1944.

201. Lyford, J., III.; Scott, R. B., and Johnson, R. W., Jr.: Polyarticular Arthritis and Osteomyelitis Due to Granuloma Inguinale, Am. J. Syph., Gonor. & Ven. Dis. **28**:588-610 (Sept.) 1944.

202. Ropes, M. W.; Rheumatoid Arthritis: Atypical Forms, Bull. New England M. Center **6**:54-56 (April) 1944.

203. Fox, M. J., and Gilbert, J.: Meningococcus Infections with Articular Complications, Am. J. M. Sc. **208**:63-69 (July) 1944.

204. Hench, P. S., and Rosenberg, E. F.: Palindromic Rheumatism, Arch. Int. Med. **73**:293-321 (April) 1944.

damage. Thirty-four cases are reported, 6 in detail. The patients had multiple inflammation, with subsidence of all symptoms between attacks. The cause was unknown. Usually the examination of the blood gave normal results, and the erythrocyte sedimentation rate was normal. Attacks provoked only transient slight elevations in the sedimentation rate. Pathologic examination of joints showed an increase in polymorphonuclear leukocytes in the synovial membrane. There might be a fibropurulent exudate. Between attacks, tissues of the joints revealed no significant evidence of inflammation. Treatment for the most part was symptomatic, usually heat and analgesics during attacks. Of 27 patients followed, 15 per cent were well, 44 per cent had improved and 26 per cent were in the same condition. Three patients were worse, and 1 had died. Not a single joint in these patients had been crippled.

[ED. NOTE.—The diagnosis of palindromic rheumatism should be made with great caution. Rheumatoid arthritis often develops slowly. I have recently seen 3 patients who had been studied in a large medical clinic and whose disease had been diagnosed as palindromic rheumatism. These patients later showed pronounced deformities and articular damage.]

Research projects have considered various phases of etiology, pathology and treatment of chronic arthritis. Waine and his associates [205] attempted to determine whether any toxic or infectious substance was excreted in the urine by patients suffering from rheumatoid arthritis. Urine from patients with active rheumatoid arthritis was passed through a filter, and 1 cc. was injected subcutaneously into the abdomens of 3 rats four times a week. Some of the urine was extracted with 70 per cent alcohol after absorption with kaolin. The extract was evaporated under a vacuum. The residuum was taken up in sterile isotonic solution of sodium chloride to make 5 cc. and adjusted to P_H 7.4. One cubic centimeter was injected into each of 3 rats. Urine was also extracted with chloroform and evaporated under a vacuum. This was taken up in sesame oil and injected into 3 rats. The animals were killed in four months. No significant lesions were found. Rosenberg and co-workers [206] report the causes of death of 30 patients suffering from rheumatoid arthritis. They found pulmonary disease the most common, causing death of 11 patients in this series. Cardiac disease was the cause for 9 patients; 7 of these patients had rheumatic heart disease. Renal disease was the cause of death of 3 patients, intestinal disease of 2, and miscellaneous causes of 5—cinchophen hepatitis, accidental death, carcinoma of the prostate, sudden unexplained death and cause unknown. The authors feel that there may be a relationship between unrecognized early rheumatic fever and the large number of deaths from cardiac disease. In only 10 of the patients was death in any way a result of the arthritis. Bayles and Riddell [207] studied the lipemia in three groups of patients with rheumatoid arthritis—10 patients receiving the usual nonspecific therapy, 11 receiving gold salt therapy and 4 whose arthritis was complicated by pregnancy. They found the total lipid, total cholesterol and phosphatide levels of the plasma and the lipid ratio normal in persons with active rheumatoid arthritis. Practically no change was noticed in the patients receiving gold salts. The lipemia of pregnant arthritic patients was similar to that of normal pregnant women. The amelioration observed on arthritis by pregnancy was not dependent on a correction of a lipid deficiency or on a shift in lipid ratios.

To determine the toxicity of gold salts, Freyberg and his associates [208] injected equivalent amounts of gold into rats, using compounds varying widely in their chemical and physical properties. They found that large doses of soluble gold salts (much larger than therapeutic doses) cause severe damage to renal tubules and glomeruli. The severity of the pathologic changes was in direct proportion to the amount of gold injected. No other organs showed important pathologic changes. Suspensions of gold in oil produced lesions in proportion to the solubility of the gold. Colloidal gold caused little renal damage, but reticuloendothelial cells packed with gold were observed in the liver and spleen after its injection. The dosage of gold could not be controlled by study of the plasma concentration of gold. In gold dermatitis, biopsies of the skin showed about the same amount of gold in the skin as was found in the skin of patients receiving gold who had no

205. Waine, H.; Bauer, W., and Bennett, G. A.: Effect of Subcutaneous Injection of Urine and Urinary Extracts from Patients with Rheumatoid Arthritis into Rats, J. Lab. & Clin. Med. **29**:19-20 (Jan.) 1944.

206. Rosenberg, E. F.; Baggenstoss, A. H., and Hench, P. S.: Causes of Death in Thirty Cases of Rheumatoid Arthritis, Ann. Int. Med. **20**:903-919 (June) 1944.

207. Bayles, T. B., and Riddell, C. B.: Plasma Lipids in Arthritis Patients Receiving Gold Salt Therapy and During Pregnancy, Am. J. M. Sc. **208**:343-350 (Sept.) 1944.

208. Freyberg, R. H.; Block, W. D., and Preston, W. S.: Gold Toxicity in Relation to Gold Salt Therapy for Rheumatoid Arthritis, J. A. M. A. **124**:800 (March) 1944.

dermatitis. Toxicity in most instances seemed to be an allergic reaction. The major factor in regard to toxicity was the speed of administration of the gold.

Turnbull [209] studied the toxicity and efficacy of massive doses of vitamin D in 30 patients with resistant chronic arthritis. The Steinbock process (ultraviolet-irradiated vitamin) vitamin D was used instead of electrically activated ergosterol (Whittier process). Toxic symptoms developed in susceptible patients and persisted as long as three weeks after the medication was stopped. In 80 per cent of the patients, toxic symptoms developed; 77 per cent were not improved in their arthritis. The author feels that electrically activated ergosterol is safer and more effective than other types of vitamin D given in large doses.

Davies [210] studied the synovial fluid in the joints of cattle between the ages of 1 and 4 years, just after they were slaughtered. He found the volume of individual joints roughly proportional to the size. Determinations of the viscosity of synovial fluid from hip and hock joints were made. The lowest value was 3.3 and the highest 575 centipoises. Values of over 150 centipoises were unusual. Forelimbs tended to have a higher viscosity than hindlimbs. Variations in viscosity were not due to variation in mucin content. The average total nitrogen content was 162 mg. per hundred cubic centimeters. Observations supported the view that synovial fluid is, at least in part, a dialysate from the blood with the addition of mucin, possibly from connective tissue.

In a study of the innervation of articular tissues Freyberg [211] found by staining with osmic acid three types of nerve endings: (1) free nerve endings, which may be on the surface of synovial cells; (2) an oval laminated end organ, usually deeper in the fibrous portion of the capsule, and (3) a fine network surrounding arterioles. No nerves were found in articular cartilage or in compact bone. All other articular structures were abundantly innervated. Pain fibers were distinct from those for touch and pressure. In patients there was a tremendous variation in the description of pain, although there was only a slight variation in the individual threshold for pain.

Sprague and McGinn [212] found that rheumatic fever and acute arthritis accounted for 0.38 per cent of the casualties and that rheumatic fever alone accounted for approximately 0.17 per cent, and combined with arthritis 0.33 per cent, of all causes for evacuation of men from the South Pacific area. Fatigue, exposure and infection of the upper respiratory tract were the activating mechanisms in bringing on an attack. They found that rheumatic fever existed among the natives of the tropics.

S. A. Goldberg [213] studied surgical and autopsy material to determine the earliest changes which appeared in chronic arthritis. The first changes in rheumatoid arthritis were in the synovial membrane and periarticular tissues, followed by changes in the articular cartilage and bone. The earliest changes were rarely seen in human beings but could be observed in laboratory animals. The characteristic changes in degenerative arthritis were in the articular cartilage. There was first a thickening and softening of the cartilage cells. This was followed by fraying and degeneration.

In a general paper Bach [214] discusses the medical treatment of rheumatic disease. In every case, social and economic factors played an important part in the development. Bach's plan of treatment consisted in four to six weeks of hospitalization in an attempt to arrest the disease and prevent crippling. Rest and relaxation were the first part of the treatment. Exercises in bed were given to induce relaxation, to improve thoracic capacity and to improve body mechanics. Casts were used to correct deformity. General irradiation and iontophoresis of the affected joints were carried out. Drugs, usually acetylsalicylic acid, were used to relieve pain and to correct any physiologic disturbance. Gold salts were given if the sedimentation rate was high; toxic manifestations were avoided. A diet which was adequate in protein and which was not too bulky was given, usually about 2,000 calories. As the patient improved, class exercises and remedial occupational therapy were given. Usually there was a long period of convalescence before the patient returned to work.

209. Turnbull, J. A.: Study of One Hundred and Twenty-Seven Cases of Arthritis, Am. J. Digest. Dis. **11**:122-130 (April) 1944.

210. Davies, D. V.: Volume, Viscosity and Nitrogen Content of Synovial Fluid, J. Anat. **78**:68-78 (April) 1944.

211. Freyberg, R. H.: Symposium on Analysis and Interpretation of Symptoms: Joint Pain, Clinics **2**: 1586-1619 (April) 1944.

212. Sprague, H. B., and McGinn, S.: Rheumatic Fever and Acute Arthritis as Causes for Evacuation from South Pacific Area, U. S. Nav. M. Bull. **43**:1-3, (July) 1944.

213. Goldberg, S. A.: Pathology of Osteoarthritis, Am. J. Clin. Path. **14**:1-23 (Jan.) 1944.

214. Bach, F.: Management of Early Arthritis, Practitioner **152**:20-25 (Jan.) 1944.

[ED. NOTE.—This is a well considered program for treatment in early rheumatic disease. Treatment cannot be standardized because of the multiplicity of possible causes and complicating factors, but a general outline such as this is helpful. Unfortunately, physicians now get patients late in their disease, when a long period of medical and surgical rehabilitation is required. It will probably require a long period of lay and professional education before this program can be applied effectively.]

In therapeutic attempts against chronic arthritis, the newer antibiotic substances have been used, with indifferent success. Boland and his collaborators [215] report on the use of penicillin in the treatment of active rheumatoid arthritis in an army hospital. In rheumatoid arthritis hemolytic streptococci have always been under suspicion. The blood usually contains antibodies against streptococci, usually agglutinins, in high titer. The skin is usually hypersensitive to extracts of hemolytic streptococci. Ten men were treated for whom the diagnosis of rheumatoid arthritis was definite and in whom the damage was not so severe that irreversible changes in the articular tissues had taken place. These patients were given 1,200,000 to 3,200,000 Oxford units daily. The penicillin was given every three hours for from fourteen to twenty days. There were no untoward reactions, and the changes observed were slight. In 8 patients there were no subjective or objective changes. One patient felt worse. In 1, slight subjective improvement was found. In 1, there was moderate subjective and objective improvement. Results of laboratory tests, including leukocyte count, sedimentation rate and cultures and smears for bacteria in the synovial fluid remained unchanged. The appetite improved in 6 of the 10 patients. The authors felt that penicillin was not of value in the treatment of rheumatoid arthritis.

Powell and Rice [216] used penicillin in treatment of rats which had arthritis caused by a pleuropneumonia-like organism. Treatment with penicillin was ineffective. Gold sodium thiomalate (Myocrysine) was effective in controlling the arthritis but was extremely toxic to the laboratory animals.

Rawls [217] used small doses of gold thioglucose (Solgonal B oleosum), which contained 50 per cent gold, for 100 patients. Five milligrams was given twice a week for three weeks, 10 mg. twice a week for the next three weeks and then 25 mg. once a week. In 42 per cent of the patients toxic symptoms developed. Half of these occurred before 100 mg. of gold had been given. The patients quickly recovered from toxic symptoms in such small doses. The severity and duration of toxic symptoms depended on the dosage. There were no fatalities. In 53 per cent of the patients there was pronounced improvement, with almost complete remission of symptoms. Twenty-one per cent were definitely improved; 12 per cent were slightly improved.

Kennedy [218] used subcutaneous deposits of a sulfonamide compound in powder form in treatment of chronic infectious arthritis. He believes that in chronic rheumatoid arthritis the affected joints and lymph glands become metastatic septic foci. For these patients he uses a drachm (3.9 Gm.) or more of sulfanilamide powder subcutaneously in the affected limb. He states that improvement was observed in 3 chronic cases.

Neostigmine to relieve muscular spasm in rheumatoid arthritis was used by Trommer and Cohen [219] on 19 patients. One cubic centimeter of neostigmine methylsulfate (in a dilution of 1:2000) and 0.6 mg. of atropine sulfate were given every other day. In addition 7.5 to 45 mg. of neostigmine bromide with 0.6 to 1.2 cc. of tincture of belladonna were given daily. Thirteen patients showed decreased muscular spasm, and motions were carried out more readily. The effect following injection comes on in fifteen minutes and may last several days. [ED. NOTE. —The editor has observed the effect of neostigmine in similar dosage on a large number of patients during the past two years. Any beneficial effect observed was slight and transient. No lasting benefit was observed from its use.]

The chronically swollen, painful joint is one of the greatest problems in arthritis. Crowe [220]

215. Boland, E. W.; Headley, N. E., and Hench, P. S.: Treatment of Rheumatoid Arthritis with Penicillin, J. A. M. A. **126**:820-823 (Nov. 25) 1944.

216. Powell, H. M., and Rice, R. M.: Ineffective Penicillin Chemotherapy of Arthritic Rats Infected with Pleuropneumonia-Like Organisms, J. Lab. & Clin. Med. **29**:372-374 (April) 1944.

217. Rawls, W. B., and others: Analysis of Results Obtained with Small Doses of Gold Salts in Treatment of Rheumatoid Arthritis, Am. J. M. Sc. **207**:528-533 (April) 1944.

218. Kennedy, R. T.: Chronic Infective Arthritis and an Experiment with Subcutaneous Deposits of Sulfonamide Powder, M. J. Australia **1**:150-152 (Feb. 19) 1944.

219. Trommer, P. R., and Cohen, A.: Neostigmine in the Treatment of Muscle Spasm in Arthritis and Associated Conditions, J. A. M. A. **124**:1237-1239 (April 29) 1944.

220. Crowe, H. W.: Treatment of Arthritis with Acid Potassium Phosphate, Lancet **1**:563-564 (April 29) 1944.

states that the articular fluid in chronic synovitis is alkaline, while it is acid in acute inflammation of the joint. To decrease swelling, a 1 per cent solution of acid potassium phosphate in isotonic solution of sodium chloride was injected into two hundred and eighty-four swollen joints. All the swellings were caused by rheumatoid arthritis except six, which were caused by traumatic synovitis. Twenty cubic centimeters was injected into the larger joints. Nine of fourteen joints with chronic swelling cleared up after one treatment. Lasting improvement was obtained in three fifths of the cases, and temporary relief was seen in all except 1, in which the condition became worse after the injection.

Mantha [221] combined gold sodium thiomalate with theobromine and sodium salicylate. Thirty-five patients had been treated. He gave 0.003 Gm. of myocrysine every ten to fourteen days and a capsule of 30 grains (2 Gm.) each of theobromine and sodium salicylate three times a day before meals. Good results were obtained by this combination.

Lawson [222] advocates large doses of salicylates for multiple rheumatoid arthritis (Still's disease). For 14 children, 85 to 293 mg. per kilogram were given. Plasma levels of 300 mg. per cubic centimeter were maintained. Six daily doses were given. Nausea, vomiting and acidosis developed in 1 child. Two children had tinnitus after therapy by intravenous injections. There was a slight prolongation of prothrombin time in all patients receiving salicylates. Four children with Still's disease showed remarkable improvement, which continued as long as the salicylate level remained high. One and one-half grains (0.09 Gm.) per pound (0.5 Kg.) was given daily, with one-third as much sodium bicarbonate. The dosage was increased if the plasma levels did not rise above 250 mg. per cubic centimeter. After clinical evidence of activity was absent for two weeks, the salicylates were stopped.

Recovery from multiple arthritis complicated by amyloidosis was reported by Trasoff and colleagues.[223] To a girl of 14, with low grade fever, palpable spleen and liver and a positive result of a congo red test, powdered whole liver was given for a number of months. The liver and spleen became no longer palpable, and laboratory findings became normal.

221. Mantha, L.: Combination of Sodium Gold Thiomalate and Theobromine with Sodium Salicylate, Union méd. du Canada **73**:271-272 (March) 1944.

222. Lawson, R. B.: Salicylate Therapy for Still's Disease, North Carolina M. J. **5**:477-482 (Oct.) 1944.

223. Trasoff, A.; Schneeberg, N., and Scarf, M.: Recovery from Multiple Arthritis Complicated by Amyloidosis in Child, Arch. Int. Med. **74**:4-10 (July) 1944.

Douthwaite [224] advocates the use of bismuth in place of gold for certain patients. In 70 per cent of 200 patients treated with gold salts, symptoms and signs of arthritis disappeared, but relapses occurred in six months in the majority of the patients. Four courses of 0.8 Gm. each within two years seemed to eradicate the disease in 55 per cent. While gold is relatively effective, the great objection to its use is its toxicity. It probably acts by virtue of its being a heavy metal. Douthwaite began using bismuth, a less toxic heavy metal, in 1942. Twelve patients were given 0.2 Gm. of bismuth weekly, receiving 2 Gm. in ten injections. All these patients had clinically active disease and an elevated sedimentation rate. In 4, all evidence of the disease disappeared and the sedimentation rate became normal. In 2 good results were obtained; moderate improvement was observed in 4, and 4 showed no response to the bismuth. Most of these patients had a relapse in a few months. The authors felt that bismuth was beneficial but not so useful as gold. It was not of value for patients who failed to respond to gold. Its chief use was for those patients who could not tolerate treatment with gold.

Levinthal and his associates [225] discussed the organization of an arthritic clinic. For arthritis many varied therapeutic procedures are necessary. Every disability which the patient presents should be considered. Orthopedic management concerns itself with correcting anatomic derangement by the usual orthopedic procedures. Medical management concerns itself with upbuilding measures and with special therapy. The authors mention two: large doses of vitamin D, which is used when the disease has been present two or more years, and gold salts, which are used in the early cases.

Physical therapeutic measures in the treatment of arthritis are described by Snow.[226] In the treatment the physician must consider the psychologic status, the pain and disability, the prognosis and the patient as a whole. The types of physical therapy include moist heat, dry heat, massage, passive movement, rest, light, electrical modalities and exercise. The type and amount depend on the stage of arthritis. This therapy

224. Douthwaite, A. H.: Treatment of Rheumatoid Arthritis with Bismuth, Brit. M. J. **2**:276 (Aug. 26) 1944.

225. Levinthal, D. H.; Logan, C. E.; Kohn, K. H., and Fishbein, W. I.: Practical Management of Arthritis—Medical and Orthopedic, Indust. Med. **13**:377-386 (May) 1944.

226. Snow, W. B.; Relation of Physical Therapy to Arthritis, New England J. Med. **229**:959-965 (Dec. 23) 1943.

must be followed carefully and carried out by skilled technicians. It is of great help but of itself does not cure.

The role of surgical measures in the treatment of chronic arthritis is discussed by Colonna.[227] The orthopedic surgeon should be responsible for the prevention of deformity and the correction of whatever deformity has developed. In the hip, deformity develops in flexion and adduction, and osteotomy is sometimes required. In the knee the deformity is commonly flexion. An appreciation of the mechanical factors leading to deformity and the mechanical derangements induced by deformity is of prime importance in the rehabilitation of such patients.

A number of papers have considered the diagnosis, complications and treatment of gout.

Sézary and co-workers[228] state that gout is rarely localized to the extremities. They report on a patient in whom deposits of urates provoked inflammatory responses and required removal. [ED. NOTE.—Faulty diagnosis for such deposits is common until pathologic examination reveals their true character.]

Bauer and Klemperer[229] discuss the medical management of gout. Hyperuricemia may result from decreased destruction, increased formation or decreased elimination of uric acid. In gout it is probably due to limitation of renal excretion of uric acid. Hyperuricemia is not the sole cause of deposition of urates in the tissues. The physiochemical factors which initiate the precipitation of urates are unknown. One cannot use determinations of serum uric acid levels as a measure of the efficiency of treatment, nor can they be used to predict an attack of gout. Colchicum is the drug of choice, but how it acts is unknown, since it does not decrease the hyperuricemia. In the treatment of acute gout, the preliminary use of a saline cathartic is recommended. Colchicine, 0.5 mg., should then be given every hour until relief of symptoms or toxic symptoms appear—diarrhea, nausea and vomiting. Then one to two doses should be given daily. Fluid, 3,000 to 4,000 cc., and rest in bed should be given. Moist heat over the affected joint is helpful. The prevention of subsequent attacks is difficult; a low purine diet or a fat-free diet is ineffective, and a normal diet is not harmful. As far as can be determined, overindulgence in alcohol does not provoke an attack. Sézary and his colleagues advocate balanced diet, avoidance of foods with high purine content and avoidance of obesity. Colchicine, 0.5 mg. three times a day, with high fluid intake, a high carbohydrate diet and maintenance of an alkaline urine are recommended for long periods. Salicylates, however, are the safest drugs. Acetylsalicylic acid, 5 to 6 Gm. a day, may be used three days a week. This leads to the rapid excretion of uric acid. Attacks cannot be prevented by the continuous use of salicylates. Chronic gouty arthritis is least amenable to treatment. Here pain is due to permanent articular changes. Gout receives no special benefit from spa treatment. The cardiovascular and renal complications are not preventable and must be treated as they appear.

Bartels,[230] in an analysis of the cases of 14 patients with chronic gout, found during an eleven year period an average loss of twenty months from work, an average salary loss of $3,640 and medical expenses of $498. In order to prevent such losses, an interval treatment has been planned. This consists of a diet low in purine and fat and high in carbohydrate, with the periodic administration of cinchophen, 7½ grains (0.48 Gm.) three times a day for three days in the week. No alcohol is permitted. Since this diet is low in vitamins A and B, these vitamins are added. At times physical therapy is helpful. Thirty-one cases were studied in detail while the patients were on this regimen. Only seven minor attacks occurred, as compared with eighty-four major attacks during an equal period before treatment.

227. Colonna, P. C.: Role of Surgery in the Chronic Arthritic Patient, Clinics **2**:955-965 (Dec.) 1943.

228. Sézary, A.; Boulenger, P., and Malanjeau, P.: Panaris, Presse méd. **50**: 386-387 (June 10) 1942.

229. Bauer, W., and Klemperer, F.: Medical Progress in Gout, New England J. Med. **231**:681-685 (Nov. 16) 1944.

230. Bartels, E. C.: Successful Treatment of Gout, J. Tennessee M. A. **37**:5-9 (Jan.) 1944.

IX. INFANTILE PARALYSIS

PREPARED BY C. E. IRWIN, M.D., WARM SPRINGS, GA.

Etiology.—Zahorsky's[231] chief purpose is to recall the experiments made by Dr. E. W. Saunders, who thirty years ago proposed his revolutionary hypothesis on the causation of acute anterior poliomyelitis. This hypothesis, as Dr. Saunders stated, was only a "working hypothesis," to be refuted or corroborated by

231. Zahorsky, J.: Saunders' Theory on the Etiology of Poliomyelitis, J. Missouri M. A. **41**:162-164 (Aug.) 1944.

future clinical observations and laboratory experimentation. Briefly stated, Dr. Saunders' hypothesis was this: Poliomyelitis in its sporadic appearance has an aviary origin through the medium of the green fly (Lucilia caesar) as a host. In other words, poliomyelitis is conveyed by the ova or larvae of the green fly from a fowl or other animal which has died from a specific paralytic disease. Not only chickens but fowls of every species are affected by limberneck. The experiments of Dr. Saunders definitely proved that the larvae of the green fly or other species of blow flies developing on a fowl dead from limberneck produce symptoms of paralysis when ingested by other animals (young fowls or guinea pigs). The author states that the clinical experience in a large number of epidemics in the last thirty years has not refuted any of the clinical data collected by Dr. Saunders, and he wishes to call attention to Dr. Saunders' published articles, which contain many suggestive avenues of approach to experimental medicine.

Transmission.—Bortagaray [232] reports on the most recent poliomyelitis epidemic in Argentina. He states that there was an increased incidence of poliomyelitis observed in Argentina from 1942 to 1943 and also an increase in the more serious type of disease in adults and older children. He states that after use of the treatment prescribed by Sister Kenny there were fewer and less severe sequelae, deformities were fewer or less pronounced, the skin appeared more normal and the muscles and bones developed more normally. The immediate results of this treatment were excellent, with a high percentage of cures in the cases of the usually fatal bulbar type. General care included rest, doses of phenobarbital sodium every four hours, small doses of morphine and infusions of dextrose or isotonic solution of sodium chloride given intravenously. The respirator was needed less frequently, as there were fewer pure respiratory paralyses. Repeated spinal punctures relieved headaches and meningeal symptoms.

Walters [233] studied 100 cases of poliomyelitis from July 1 to Nov. 15, 1943 to determine the incidence of certain epidemiologic factors for this article. The report is as follows:

Twelve per cent of the patients had been swimming in water which may have been contaminated with sewage. This was not considered an important factor in the cases studied.

Use of water from shallow wells and use of no other sanitary facilities than privies were surveyed. Thirty-six per cent were regular users of well water, 11 per cent used cistern water and 2 per cent had used spring water; 54 per cent lived within 100 yards (90 meters) of one or more outdoor toilets.

In line with Aycock's conclusion that milk-borne epidemics of poliomyelitis are probably of the same frequency as epidemics of other infectious diseases which are occasionally transmitted through milk, 68 per cent had used raw milk for an indefinite time prior to their illness.

The high incidence in proximity of chickens to poliomyelitis victims noted in the study bears out Hammon's belief that the rural barnyard and the fowls of the semirural home are the chief sources of infection. Eighty-nine per cent of the patients surveyed had chickens on their own premises or within 100 yards of their homes. Sabin and Ward had concluded, after investigating the virus in insects, "We believe that the search for a reservoir of poliomyelitis virus among the lower animals is worth while and should continue. . . . We are inclined to regard poliomyelitis as a disease which occurs the year round but has a greater incidence during the summer and autumn because greater dissemination of the virus may be made possible by a number of factors, including insects such as flies." In Walter's study 12 per cent of patients lived within 100 yards of sheep or goats, 32 per cent owned or lived within 100 yards of horses, 38 per cent were within the same distance of hogs and 48 per cent within a similar distance of cows, 48 per cent owned cats, 59 per cent possessed dogs, 83 per cent acknowledged the presence of flies on their premises and 62 per cent had mosquitoes on their premises.

Ward and Melnick [234] state that the aim of their communication is not to make a plea for sewage or flies as vehicles in the transmission of the disease but to point out that contact infection has not been demonstrated to be the "most important means" of spreading poliomyelitis. It seems futile to insist on a "unitarian" theory of spread.

Virus has been kept in sewage at a temperature of 7 C. up to eighteen days. Low concentrations of residual chlorine destroy a fixed amount of Theiler's mouse poliomyelitis virus. This same amount of virus in the presence of extrane-

232. Bortagaray, M. H.: Most Recent Epidemic of Poliomyelitis in Argentina, Rev. Soc. puericult. Buenos Aires **9**:413-418 (Oct.-Dec.) 1943.

233. Walters, O. S.: Possible Transmission Factors in Poliomyelitis, J. Kansas M. Soc. **45**:163 (May) 1944.

234. Ward, R., and Melnick, J. L.: Spread of Infantile Paralysis, J. A. M. A. **124**:595-596 (Feb. 26) 1944.

ous organic matter survives more than ten times this amount of residual chlorine.

Arguments against flies playing a role in transmission are as follows: 1. Flies are not invariably associated with the disease, as in winter poliomyelitis. 2. The disease would not attack children preponderantly, as is the case, if it were transmitted primarily by the fly or any other insect. One would expect just such a high incidence in children if adults were immune because of infection—preponderantly abortive or nonparalytic—acquired in childhood or immunity acquired by other, as yet unrecognized, means.

The probability of obtaining virus from flies trapped in epidemic areas would appear to be as good as that of obtaining it from stools and certainly better than that of finding it in nasopharyngeal washings.

Contact infection is admittedly a means of spread, but that it is "the most important means" has not been proved to the authors' satisfaction. Seasonal incidence cannot be explained in this way (epidemics fade out when school opens). The rarity of hospital infection from patient to patient and from patient to hospital personnel would militate against the philosophy of greater segregation as a solution, or even as an aid to a solution, to the problem.

The authors express the belief that it is wise to keep receptive minds to evidence which may eventually show other "modes of spread of infantile paralysis," more in keeping with present knowledge of the natural history of the disease.

Horstmann, Ward and Melnick [235] undertook a study to determine the average duration of excretion of virus in stools of patients following acute infection and to ascertain whether a chronic carrier state similar to that occurring in typhoid exists in poliomyelitis. The stools of 61 patients (46 paralytic and 15 nonparalytic) were collected during the first or second week of the disease and at four to six week intervals thereafter. The materials collected were frozen immediately or within a few hours after collection and stored on solid carbon dioxide until ready to be tested. The inoculum (prepared by Melnick's technic with a few minor changes) was ultracentrifuged at 39,000 revolutions per minute and inoculated into immature rhesus monkeys, by the intracerebral route in fifty-four tests, directly into the lumbar portion of the cord in eighty tests and by a combination of the two routes in twelve. All but 2 monkeys were ultimately killed, and the result of a test considered positive when microscopic lesions characteristic of poliomyelitis were seen in the spinal cord. It was found that 61 per cent of the patients excreted virus during the first two weeks after onset of the disease, 50 per cent during the third and fourth weeks, 27 per cent during the fifth and sixth weeks and 12.5 per cent during the seventh and eighth weeks. Between the ninth and twenty-fourth weeks, virus was detected in only 1 of 52 specimens tested, 1 patient excreting it in the twelfth week. Not one of the 61 patients followed was demonstrated to become a persistent carrier of poliomyelitis virus.

Maxcy [236] states that present day conceptions of epidemiology of poliomyelitis rest in a large part on the observations made in Norway and Sweden toward the end of the nineteenth century and during the early part of this century, which are available in the classic monograph of Ivan Wickman, published in English translation in 1913. Studies in the United States began with the reports of Dr. Charles S. Caverley on the occurrence of anterior poliomyelitis in the state of Vermont in 1894 and were continued by Flexner and Lewis after the 1907 epidemic in New York and by W. H. Frost after the 1910 outbreak in Minnesota and Nebraska, the 1911 occurrence in Iowa, the outbreak in Cincinnati in 1911 and in Buffalo and Batavia, N. Y., in 1912. The largest epidemic which this country has experienced occurred in and about the city of New York in 1916 and was studied in great detail by three officers of the United States Public Health Service, C. H. Lavinder, A. W. Freeman and W. H. Frost. Since the publication of their report, the large number of contributions from investigators in this county and abroad have served to confirm, amplify and extend the basic observations, although the net advance has been relatively small.

After review of available morbidity and mortality data, with considerations of their limitations in mind, the following brief interpretations regarding broad general characteristics appear to be valid:

1. The disease is worldwide in distribution.

2. From no human community is the disease long absent.

3. Transmission can occur in any month of the year.

235. Horstmann, D. M.; Ward, R., and Melnick, J. L.: Persistence of Virus Excretion in the Stools of Poliomyelitis Patients, J. A. M. A. **126**:1061-1062 (Dec. 23) 1944.

236. Maxcy, K. F.: A Review of the Epidemiology of Acute Anterior Poliomyelitis with Reference to the Mode of Transmission, Journal-Lancet **64**:216-223 (July) 1944.

4. The disease exhibits an irregular interanunual periodicity in prevalence.

5. From an original focus, the spread is progressive in unpredictable directions.

6. It has no regular pattern as regards rural and urban distribution if long periods are considered.

7. Poliomyelitis is characteristically a disease of early childhood.

8. Immunity to attack is acquired with advancing age.

9. The total number of patients manifesting characteristic paralysis during an epidemic period rarely exceeds 2 per thousand population of all ages.

10. The number of persons infected with the virus of poliomyelitis is far greater than is indicated by an attack rate based on reported cases of paralysis alone.

11. A considerable proportion of patients has had recent direct or indirect contact with a person who is known or suspected to have or to be convalescing from a paralytic or nonparalytic stage of the disease.

After illustrating the behavior of poliomyelitis in two local outbreaks (the first in Atlanta, Ga., in 1941 and the second in a small rural focus in the state of New York in 1940), the author states that the interpretation which seems most consistent with the facts and observations presented up to this point may be briefly summarized as stated by Lavinder, Freeman and Frost in 1916:

1. That poliomyelitis is, in nature, exclusively a human infection transmitted from person to person without the necessary intervention of a lower animal or insect host, the precise mechanism of transmission and avenues of infection being undetermined.

2. That the infection is far more prevalent than is apparent from the incidence of clinically recognized cases, since a large majority of persons infected become "carriers" without clinical manifestations (i. e., have had inapparent infections). It is probable that during an epidemic such as that in New York City a very considerable proportion of the population becomes infected, adults as well as children.

3. That the most important agencies in disseminating the infection are the recognized carriers and perhaps mild abortive cases ordinarily escaping recognition. It is fairly certain that the frank, paralytic cases are a relatively minor factor in the spread of infection.

4. That an epidemic of one to three recognized (i. e., paralytic) cases per thousand, or even less, immunizes the general population to such an extent that the epidemic declines spontaneously, due to the exhaustion or thinning out of infectible material. Apparently an epidemic incidence relatively small in comparison to that prevailing in an epidemic may produce a population immunity sufficient to definitely limit the incidence rate in a subsequent epidemic.

After examining the literature on the question of transmission, Maxcy says that it is uncertain whether the effective exit of the parasitic virus is via oropharyngeal secretions or by feces or by both. He analyzes the data available on transmission of fecal-borne pathogen by persons, flies and water, and he gives the technic used in establishing and then partially abandons the hypothesis of transmission by secretions of the oropharynx. His final conclusions are that it is within the realm of possibility that both mechanisms of transfer—the respiratory contact and the fecal contact—are operative and that each plays a role in maintaining passage of the virus through human populations.

Biermann and Piszczek[237] report on a case of poliomyelitis in a newborn infant in the epidemic of 1943 in Wichita, Kan. The mother had an uncomplicated pregnancy, with normal delivery. The onset of fever (temperature 100.6 F.) occurred eleven hours following delivery, with typical symptoms of acute poliomyelitis ensuing. There was complete paralysis of both upper and lower extremities, along with bulbar involvement. The patient became progressively worse and died on the fourth day post partum. The child (a normal boy) was seen by the mother for ten minutes four hours after delivery. The degree of contact was not observed. The child was normal until the eleventh day of life, when he became listless, febrile and cyanotic. The diagnosis of poliomyelitis was substantiated by laboratory observations, including study of the spinal fluid. Both upper and lower extremities and abdomen were involved at first, and later general improvement was noted but the right lower extremity continued paralyzed.

There were 164 persons who had the disease in the county in which this patient resided, 9 of these in the town district (the mother was the seventh and the child the eighth). The father and two other children were well throughout the mother's illness.

The authors state that the possibilities of infection in this case were: (1) fetal infection, (2) birth canal exposure, (3) contact exposure and (4) other contact exposures. In the absence of laboratory evidence that contacts of the child other than the mother were excreting poliomyelitis virus, it was, of course, impossible to determine the source of the infant's infection; however, it appeared to them that the available evi-

237. Biermann, A. H., and Piszczek, E. A.: A Case of Poliomyelitis in a Newborn Infant, J. A. M. A. **124**:296-297 (Jan. 29) 1944.

dence suggested that infection occurred at time of birth or shortly thereafter.

Krumbiegel,[238] in discussing the transmission of virus diseases (specifically poliomyelitis) by water, states that pathogens causing communicable diseases known to be spread by water usually enter the body via the gastrointestinal tract and leave in feces or urine or both. Accumulated weight of evidence points toward the gastrointestinal tract as the probable portal of entry, and there are an increasing number of investigators leaning toward the belief that, although poliomyelitis is essentially a disease affecting the central nervous system, it may be a "digestive tract disease" in that the virus may enter the body through one end of the tract and leave by way of the opposite end. Virus is found repeatedly in stools during the second and third weeks of convalescence following paralytic or abortive attacks. Stools are known to have contained virus for as long as one hundred and twenty-three days. The virus is exceedingly stable, surviving a 50 per cent solution of glycerin for eight years, and it withstands low dilutions of phenol and 15 per cent ether. It is not surprising, therefore, that it may be demonstrable in sewage. The activated sludge method of treating sewage is effective in removal or destruction of the virus of poliomyelitis. The virus remains active for as long as one hundred and fourteen days in sterile water at room temperature in the dark. It also withstands freezing. Coagulation and sedimentation seem to produce a slight reduction in the total amount of virus in any suspension, proportional to the amount of virus present. Sand filtration has little if any effect. The addition of activated charcoal to the suspension is partly effective, and the addition of alum floc to the suspension greatly reduces the amount of virus. Chlorination studies are inconclusive, as they were not comparable to methods employed by water purification plants. To date, epidemiologic evidence fails to indicate that water is biologically of any importance as a medium of transmission. It would be necessary to show that the behavior of poliomyelitis in some places or at some times is dependent on contaminated water. This has never been done, and the known epidemiologic behavior of the disease is definitely not compatible with a theory of water-borne spread. Cold is not deleterious to the virus; hence, if water borne, poliomyelitis should occur commonly in winter months. Usually epidemics occur in scattered regions with no common water supply. If the disease were water-borne, there should be an explosive onset with large numbers of cases, which is not the case. The prevalence of the disease has not been correlated with the degree of sanitary care surrounding different water supplies as determined by either bacteriologic examination or sanitary survey.

Casey and Hidden [239] give a most interesting account of George Colmer III (Kolmer; Sept. 21, 1807-Sept. 27, 1878), a physician who was born in London, England, but who resided at Springfield, Livingston Parish, La., from 1841 until his death, except for a short period when he had an office in New Orleans. His recently discovered "Diary C" covers the period from 1849 to 1878 ("Diaries A and B" have not been found) and records local and national events, clippings from medical and lay journals, pamphlets and advertisements, daily and careful observations on weather, flood stages, flowering of various plants, occurrence of various epidemics, local meetings and local news, such as births, deaths and marriages, observations on garden vegetables, fishing, prize-winning stocks and crops. Another volume, the daily journal of his medical practice from about 1842 to 1878, records brief abstracts of the history, physical examination and treatment of his patients, including two pages of periodic notes on his own physical condition. Dr. Colmer was civic minded and did much for his community, including the building and running of a slave hospital in which the daily board was $1 and the medical fees in accordance with the malady. His greatest contribution, however, seems to be his observations on the epidemiology of poliomyelitis. Paralysis in children was noted in Philadelphia in 1792 during an epidemic of yellow fever, and 4 cases were noted by Badham in Workshop, England, in 1835. The pathologic changes of poliomyelitis were first described by Heine in 1840, but the first epidemic of the disease to be reported anywhere in the world occurred in 1841 in West Feliciana Parish, La., some 30 miles (48 Km.) from Springfield, La., and was published in *The American Journal of the Medical Sciences* by Dr. Colmer in 1843. His observations that the disease occurred in the form of an epidemic in a small rural area in late summer and fall, that it largely affected children of the teething age (1 to 2 years), that it was associated with paralysis and that most of the youngsters eventually recovered have not been much improved on during the past hundred years. His additional note that teething

238. Krumbiegel, E. R.: Transmission of Virus Diseases by Water, Bull. Hyg. **19**:513 (July) 1944.

239. Casey, A. E., and Hidden, E. H.: George Colmer and the Epidemiology of Poliomyelitis, South. M. J. **37**:471-477 (Sept.) 1944.

was probably a factor may also be apt, as the drooling saliva is probably infectious in the several days before the onset of the prodromal period. If "Diary B" could be found or the daily journal of his medical practice before 1842, the epidemic would probably have also been described in them in greater detail, as Dr. Colmer was an efficient reporter of other local events.

Diagnosis.—Pounders [240] gives a comprehensive report on the diagnosis and medical management of poliomyelitis. The onset usually occurs with mild general symptoms accompanied with disturbances of the upper respiratory and digestive tracts lasting twenty-four to forty-eight hours. Two to four days later fever recurs, along with signs of meningeal irritation, and in one to four days later motor disturbances appear. The disease may be arrested in any stage, and in most cases it does stop short of motor involvement. Later, blood serum contains antibodies against the virus. The temperature is usually about 102 F. for four or five days. There is headache (any type), vomiting, constipation or diarrhea, urinary retention (especially the first five days or so), dizziness, irritability, pains in the back and legs and general hyperesthesia. Coarse tremor, especially of the hands, is an important diagnostic sign. The patient looks sicker than the temperature would indicate, the face is flushed and has an anxious expression and the pulse is increased out of proportion to the fever. There is inability to flex the back. Deep reflexes are exaggerated and unequal. There may be meningeal signs. The spinal fluid count reveals some increase in pressure; it may be clear or slightly hazy. The cell count averages 100 to 200 but may be 10 to 1,400. It becomes normal after ten to fourteen days. Albumin and globulin are moderately increased, and sugar is normal or slightly increased.

Muscle dysfunction appears in two to five days, usually with maximum involvement within one or two days. The temperature usually returns to normal four to six days later. The virus is active as long as the patient is febrile.

The lower extremities are usually involved, with spasm of the hamstring muscles. Later there are weakness of the quadriceps and spasm of gastrocnemius muscles, with weakness of the anterior tibial group. In the upper extremities the deltoid and shoulder girdle muscles are most commonly affected. The anterior flexors of the neck are often weak.

Respiratory difficulty may be due to (1) involvement of the thoracic portion of the cord, with dysfunction of the intercostal muscles; (2) lesions of the cervical part of the cord, in the third and fourth segments, with involvement of the diaphragm, (3) bulbar lesions involving nuclei of the vagus nerve, (4) acute ascending so-called Landry's type of paralysis showing successive intercostal, phrenic and bulbar involvement and (5) occasional pharyngeal paralysis resulting in pronounced respiratory difficulty because of excessive fatigue from the continual interference with respiration by unswallowed material in the pharynx or by actual aspiration of this material. The cranial nerve most commonly affected is the facial, and when it is the only one involved the patient is usually not very sick. In more than half the cases, the disease clears up entirely. Involvement of the third, fourth and sixth cranial nerves affecting the eye muscles is occasionally encountered.

In treatment, complete rest in bed is indicated. Sedatives to induce sleep should be used cautiously when there is evidence of respiratory or bulbar paralysis. Pain and tenderness and muscle spasm are best relieved by hot applications. The usual procedures recommended in care of a sick child are applicable—fluids, a high caloric diet of soft food and attention to elimination. The respirator should be used when indicated, but when the respiratory center is paralyzed the apparatus gives only temporary help and may even be harmful.

Murphy,[241] in making a plea for early diagnosis, states that this is imperative for best treatment. Diagnosis is largely clinical. Approximately 80 per cent of all cases in an epidemic area are so-called abortive cases. Symptoms are mainly those of an acute infection. A high titer of immune substance on virus neutralization tests is demonstrable later. During the acute febrile course of the subclinical or clinical case and the asymptomatic period of the clinical case, there are no immediate symptoms, physical findings or spinal fluid changes that are diagnostic. During summer and fall, alertness to symptoms of acute infection is necessary. Temperature ranges from 101 to 105 F., and there are headache and vomiting at the onset, constipation or loose stools, malaise and even drowsiness. Pain is inconstant (in the back, chest and abdomen); it may be due to hyperesthesia and may be sufficiently intense at times

240. Pounders, C. M.: The Diagnosis and Medical Management of Poliomytlitis, J. Oklahoma M. A. **37:** 487-489 (Nov.) 1944.

241. Murphy, J. H.: A Plea for the Early Diagnosis of Poliomyelitis, J. Omaha Mid-West Clin. Soc. **5:** 85-87 (Aug.) 1944.

to simulate other disease. The critical findings of differential diagnostic value depend on signs of cord, brain and nerve irritation and must be supported by physical findings. These are sometimes so extremely variable and changeable that they may be detected only by careful, deliberate and repeated examinations. The most important sign is nuchal rigidity, which is accompanied with or followed by spinal tenderness. Kernig's sign may appear early or not. Deep reflexes are present but variable (hyperactive to sluggish). The muscle groups or muscles presenting tremors are likely to be involved. Rigidity of muscles, deep tenderness, discrete areas of perspiration, irritation of rectal or vesical centers in the lumbar part of the cord, with resulting constipation or urine retention, all may be demonstrated. Bulbar involvement may have a rapid onset, with difficulty in swallowing, impairment of phonation, salivation and excessive mucous secretion, disorientation, delirium and coma.

Puncture of the lumbar part of the cord is of therapeutic value in reducing intracranial pressure. The spinal fluid is normal throughout the first febrile and asymptomatic stages of the disease. At the onset of the paralytic phase, the spinal fluid is clear, there is increased pressure, the cells may vary from 10 to 200, the total protein is increased and the fluid is sterile on bacteriologic examination and does not contain the virus. Hence, examination of the spinal fluid is important if the results are positive but not necessarily contradictory when values are normal. The blood count and sedimentation rate are not contributory to diagnosis. Differential diagnosis is important in acute poliomyelitis to rule out purulent meningitis, encephalitis, St. Louis encephalitis and occasionally acute arthritis. The cardinal points of early diagnosis are: (1) awareness of poliomyelitis, (2) history of febrile attack a few days previously, (3) headache and fever, (4) nuchal rigidity and spinal tenderness, (5) spasm, tremor or weakness in a muscle or muscle groups, (6) hyperesthesia or pain, (7) reflex changes and (8) cerebrospinal fluid changes if positive. The author states that (9) the serious grade of the disease is indicated by progressive course and that (10) it is impossible to diagnose subclinical cases in the acute stage.

Prevention.—Lumsden,[242] in writing on the epidemiology of poliomyelitis and measures for its prevention, states that the possibility of several specific viruses of poliomyelitis is given weight by the fact that strains of the virus obtained in different outbreaks present pronounced differences biologically, serologically, immunologically and otherwise. There are many possible modes of transmission, but none are conclusive. Preventive measures suggested are: (1) cleanliness and maintenance of cleanliness (hygiene and sanitation); (2) systematic, intense and continuous fights on rats, mice, flies, mosquitoes, roaches, fleas, bedbugs, ants, insects and vermin; (3) strict sanitation regarding disposal of garbage, manure and excreta of poultry and birds; (4) screening of living and sleeping quarters; (5) purified water supplies and sanitary sewage systems with final disposal; (6) rigid sanitary and hygienic supervision of public eating and drinking places; (7) educational campaign to discourage potential droplet infection (coughing, sneezing, spitting, blowing and wiping); (8) reasonable discouraging of public assemblages by children under 6 years, and (9) restraining of young children from undue physical stress. Closing of schools, churches and theaters, as is often demanded by misled public opinion, is unjustified; placarding of the affected homes is advisable; proper isolation of patients is advisable to guard against superimposed infections. There should be rigid disinfection of discharges from nose and mouth and feces. Quarantine is not justified except for food handlers and persons in close contact with large numbers of children.

Pathology.—Dublin, Bede and Brown[243] report their findings on studies of muscles taken for biopsy from 3 patients with poliomyelitis and stained by the Ranvier method. They observed a degeneration of nerve fibers, motor end plates and muscle fibers in a degree commensurate with the degree of paralysis; an irregularity of distribution in keeping with an irregularity of distribution of injury to nerve cells of the gray matter of the spinal cord; a degeneration of nerve fibers, consisting largely in failure of axons to stain together with preservation of cellular elements of capsules of motor endings and of sheaths of Schwann; atrophy of muscle fibers appearing as pyknosis, beginning with loss of cross striations and increase of longitudinal markings; degeneration of muscle and nerve ranking probably secondary to injury to nerve cells of the spinal cord, and no definite evidence of activity of degeneration or regeneration.

242. Lumsden, L. L.: Poliomyelitis: Its Epidemiology and Measures for Its Prevention, Texas Rep. Biol. & Med. **1**:233-241, 1943.

243. Dublin, W. B.; Bede, B. A., and Brown, B. A.: Pathologic Findings in Nerve and Muscle in Poliomyelitis, Am. J. Clin. Path. **14**:266-272 (May) 1944.

Baker [244] states that in view of the numerous and comprehensive studies on the pathologic changes of poliomyelitis by many competent pathologists one cannot hope to offer any new or startling observations on this subject. However, because of the many conflicting viewpoints regarding the significance of the various pathologic changes, it would seem of definite value to review again the histopathology in an attempt to arrive at some acceptable conclusions concerning these lesions and their significance. These conclusions are as follows: 1. A review of the literature reveals an unusual consistency in the nature of the lesions described as occurring in poliomyelitis. 2. Six illustrative cases of poliomyelitis and polioencephalitis are reviewed and discussed. 3. From these cases, the following conclusions can be made concerning the pathologic changes of this disease: (*a*) Meningitis of a mild degree is one of the earliest lesions and occurs independently of any other changes. (*b*) Mesodermal-glial (interstitial) changes comprise one of the most striking features. These changes may also occur independently of any other changes, as indicated by their appearance among both structurally and functionally intact neurons as well as by their occurrence in regions where nerve cells are normally absent. (*c*) The neuronal involvement constitutes the most important alteration because of the associated functional impairment. The damage to many of the nerve cells is reversible, with many neurons regaining normal function. Other neurons, however, are irreversibly damaged.

Complications and Sequels.—Cooperstock [245] records 4 cases of atelectasis complicating acute poliomyelitis with involvement of respiratory muscles, in 3 of which unexpected recovery took place. He believes that pulmonary infections develop secondarily to atelectasis produced by obstruction of the bronchi by unexpelled exudate. In patients with poliomyelitis with involvement of respiratory muscles, there is diminished vital capacity due not only to poor tonus of these muscles but also to poor general condition and consequently poor tonus of all muscles. There is also impaired efficiency of the cough mechanism, which permits accumulation of mucus in the bronchi and even occlusion with resulting atelectasis. Stagnant mucus is also a good medium for growing organisms natural to this region, with secondary pneumonia as a result. The prophylaxis in such cases is the avoidance of exposure to infections of the upper respiratory tract and the institution of treatment early when they occur. Use of a respirator is essential. The respiratory tract must be kept open by suction or bronchoscopy. The indication for removing such patients from respirators is not the ability to breathe freely and without effort but the ability to cough, which is the prime indication.

Wyllie [246] discusses a study concerned with a familial outbreak of poliomyelitis, which began with the introduction of facial palsy into a rural family, previously uninfected, by a single member of the family, which resulted in paralytic and abortive types of the disease in the other members.

Cranial nerve nuclei are regarded as the analogs of the anterior horn cells; hence they may be attacked by the virus of poliomyelitis. The facial nerve (seventh) is the cranial nerve most often involved. The type of facial paralysis depends on the site of the lesion.

(*a*) A supranuclear lesion produces unilateral facial paralysis, but the forehead can still be wrinkled (bilateral innervation).

(*b*) A nuclear lesion, such as occurs in poliomyelitis, results in unilateral paralysis very similar to Bell's palsy.

(*c*) A lesion between the pons and the geniculate ganglion produces flaccid unilateral paralysis of the face, usually associated with deafness due to the close proximity of the auditory nerve.

(*d*) If the lesion occurs in the facial canal below the geniculate ganglion, Bell's palsy is apt to be produced. A sensory disturbance often appearing early and transient is fairly common in poliomyelitis.

In the family outbreak a daughter visiting in the city returned home afflicted with paralysis of the right side of the face. Sixteen days later a sister had symptoms of meningitis with paralysis of the right side of the face. Thirty-six days after the sister returned home from the city a brother became acutely ill with paralysis of the abdomen and legs, and a diagnosis of poliomyelitis was made. The mother and another son suffered sharp attacks of "influenza," as they regarded it, but their symptoms were also suggestive of abortive poliomyelitis. The illnesses occurred in the period from August through October, at which time "refrigeration" of the "superficial part" of the facial nerve was unlikely. Since chills are doubtful causes of facial paralysis and a coincidental occurrence of

244. Baker, A. B.: The Central Nervous System in Poliomyelitis and Polioencephalitis, Journal-Lancet **64**:224-233 (July) 1944.

245. Cooperstock, M.: Atelectasis Complicating Acute Poliomyelitis with Involvement of Respiratory Muscles, Am. J. Dis. Child. **67**:457-462 (June) 1944.

246. Wyllie, J.: Facial Paralysis in Relation to Poliomyelitis: A Study of a Family Outbreak, Canad. J. Pub. Health **35**:71-79 (Feb.) 1944.

2 cases of Bell's palsy followed by a case of paralytic poliomyelitis in the same family is highly improbable, it is suggested that the virus of poliomyelitis may have involved the nucleus of the seventh cranial nerve, just as it is known to attack the anterior horn cells of the spinal cord. Four years after the onset of the disease, both sisters exhibited a slight residual paralysis of the face and the brother a persisting flaccid paralysis of the right leg.

That additional information might be gained on the relation of tonsillectomy to poliomyelitis the records of the Manhattan Eye, Ear and Throat Hospital were consulted, and many thousands of patients for whom tonsillectomy had been performed were communicated with by mail. Page [247] reports on these data along with the records secured from the New York Department of Health, which showed a conspicuous increase in the number of poliomyelitis cases every other year as follows: 243 cases in 1937, 43 cases in 1938, 184 cases in 1939, 67 cases in 1940 and 404 cases in 1941. Of the 27,849 questionnaires sent out from the hospital, 8,915 were answered, and 1 instance of poliomyelitis was reported. Seven patients reported illnesses following tonsillectomy and adenoidectomy, and all of these mentioned some spinal involvement; 6 reported spinal meningitis (three months to four years after operation) and 1 a "spinal condition which causes nervousness" in a child aged 6.

Howe, Wenner, Bodian and Maxcy [248] report on the different technic used for demonstrating virus in the human nose and throat, which was employed at the New Haven Hospital in the summer of 1943. The attempt to vary the method employed in the past was made, since the attempts of the earlier years have been virtually abandoned in the face of readily isolated intestinal virus. Cotton swabs rubbed against the posterior wall of the oropharynx and the peritonsillar area were dropped into a fluid-tight container with 1 cc. of sterile water, stored on solid carbon dioxide and then eluted in phosphate buffer at p_H 8, the fluid being pressed out of the cotton in a syringe. The eluate was then brought to p_H 6 and treated with 20 per cent ether in the refrigerator until sterile (usually thirty-six hours), at which time the ether was removed. The entire inoculum obtained (in no case more than 1.1 cc.) was given to rhesus monkeys of 8 to 10 pounds (3.6 to 4.5 Kg.) under ether anesthesia through a trephine hole made over the sagittal suture just posterior to the coronal sutures. An average of two swabs were obtained from 10 patients (paralytic or nonparalytic) during the first week of the acute illness. Fourteen specimens were used from the twenty collected, and seven (50 per cent) produced typical poliomyelitis in the test rhesus monkeys. Microscopic sections showed characteristic lesions in each case.

Surgical Treatment.—Debrunner [249] discusses a case of poliomyelitis in which not only organs and tissues were adapted to changed function but function itself was adjusted to changes in structure. A 4 year old girl with residual paralysis in the left leg, slight Trendelenburg position, pes cavus and pronounced paralysis in the heads of both biceps muscles and in the gluteal muscles was observed. In the foot there was a total paralysis of the anterior tibial and pronounced weakening of both other supinators. Her gait was impaired by faulty position of the foot, bearing weight only on the inner margin. She had received no planned treatment. To raise the foot, a small support was made from a plaster cast, which permitted walking in good position. After a year the support had to be altered slightly. A year later, when the mother came for repair of the support, it was noted that the impression of the sole had been changed to that of a normal foot. It is of special interest that a muscle of only secondary importance for the posture mechanism of the foot was brought into use for gait automatism. It is suggested that deformity might be prevented by training motor function.

Wiesenfeld [250] reviews the results of 17 cases of posterior bone block operations: 52.9 per cent were done by Briggs's modification of the Campbell bone block and 35.2 per cent were done by Gill's procedure. All the patients had had previous foot stabilizations. Of the series, 11.9 per cent had a combination foot stabilization, tendo achillis lengthening and posterior bone block. The results were considered excellent in 88.2 per cent of the patients operated on. There were two failures: in the first patient a painful arthritis of the ankle joint developed,

247. Page, J. R.: Tonsillectomy and Poliomyelitis, Arch. Otolaryng. **39**:323-324 (April) 1944.

248. Howe, H. A.; Wenner, H. A.; Bodian, D., and Maxcy, K. F.: Poliomyelitis Virus in the Human Oro-Pharynx, Proc. Soc. Exper. Biol. & Med. **56**:171-172 (June) 1944.

249. Debrunner, H.: A Case of Physiologic Functional Adaptation of Plantar Muscles in Residual Paralysis, Schweiz. med. Wchnschr. **73**:965 (Aug. 7) 1943.

250. Wiesenfeld, P. C.: Report of Seventeen Cases of Posterior Bone Block for Drop-Foot Seen and Treated at the New Jersey Orthopaedic Hospital, Orange, N. J., from 1933 to 1943, J. M. Soc. New Jersey **41**:344-346 (Sept.) 1944.

and the second patient was a young woman who wished to wear high heels, although the foot was blocked at a 90 degree angle. This was later revised to give her 10 degrees of flexion.

[Ed. Note.—I believe that in all cases of posterior bone block there should have been previously a stabilization by a triple arthrodesis. It appears to me that the triple arthrodesis, heel cord lengthening and posterior bone block is too much operative procedure to attempt to control at one sitting.]

Kleinberg [251] states that since there is no cure for scoliosis the treatment is consequently limited to two objectives: first, prevention of increase in deformity and, second, improvement or reduction of the curvature. Scoliosis complicating acute poliomyelitis is a more serious problem than the idiopathic and the nonparalytic curvature. The salient features that influence therapy are the following:

The plastic state of the tissue. The vertebrae become susceptible to structural alterations.

Onset. The onset is insidious.

Static imbalance. Unequal involvement of muscles of trunk and of pelvifemoral groups.

Progress of paralytic scoliosis. This may occur slowly or progress rapidly after a period of several years. It may increase after a seemingly adequate vertebral fusion.

Trophic changes. These occur in bones and are due to disturbed innervation and poor circulation.

Unknown etiologic factor. The etiologic factor is unknown.

Incidence. The incidence was 10 per cent in the author's cases and 30 per cent in the cases of Colonna and Von Saal.

Sex distribution. Cases were about equally distributed between the sexes.

Time of onset of paralytic scoliosis. In 50 per cent of cases the onset occurred in the first five years after the illness.

Muscle paralysis. About 75 per cent of the patients had involvement of abdominal muscles, with convexity of curve on weakened side.

Types and degrees of curvature. Two thirds of 34 patients had a single long curve involving most or all the dorsal and lumbar vertebrae. In 80 per cent the curvature was severe; many had "razor back" deformities.

Treatment applied. Myotomies, tenotomies, astragalectomies, Hoke stabilizations, arthrodeses, osteotomies of all types, leg lengthening, abdominal fascial reenforcements and spinal fusions were performed, and all attributed to use of limbs and security in standing and walking.

Results of spinal fusions. Eighty per cent failure was encountered in correcting the scoliosis or preventing increases. This may be attributed to delay in fusion, insufficient number of vertebrae fused and pseudoarthrosis in a few.

The prophylaxis of paralytic scoliosis includes (1) early recognition of deformity; (2) maintenance of symmetry of trunk; (3) support of the back by canvas corset, celluloid jacket, brace or plastic jacket; (4) reconstructive surgical treatment, which should be done as soon as the phase of spontaneous recovery has passed; (5) exercises, and (6) fascial reenforcement of the abdominal wall. This should be done early, as it has little if any value after severe scoliosis develops.

The treatment of scoliosis involves two features: (1) reduction of curvature, for which the author uses traction on the head and pelvis with the patient recumbent on a convex frame, and (2) spinal fusion, which should be contemplated as soon as scoliosis is discovered. Fusion should extend from the upper to the lower transitional vertebrae of the improved spine in a single curve or from the uppermost transitional vertebra to the lowermost in compound curves. Rest in bed (two to three months) should follow until fusion is solid. Then the back should be supported by a plastic jacket, corset or brace for several years.

Kleinberg [252] describes an extra-articular operation for correction of paralytic genu recurvatum. He employs two Steinmann pins for control of the fragments, one passed transversely through the distal end of the proximal fragment and the second one through the middle third of the tibia for control of the lower fragment. Osteotomy of the fibula is done 2 inches (5 cm.) below the neck, and the transverse osteotomy of the tibial shaft is done about 1½ inches (12.7 cm.) below the tubercle. The distal fragments are flexed; the upper fragments, maintained in hyperextension. A cast is applied incorporating both pins. Kleinberg summarizes the advantages of the procedure as follows:

1. The operative manipulation is completely extra-articular.

2. The surgery does not invade the knee joint and does not disturb its normal mechanism by taking away the patella.

251. Kleinberg, S.: Paralytic Scoliosis: An Analysis of Fifty-One Cases, Am. J. Surg. **64**:301-312 (June) 1944.

252. Kleinberg, S.: The Operative Correction of Paralytic Genu Recurvatum, Bull. Hosp. Joint Dis. **5**: 43-51 (April) 1944.

3. The technique does not use a bone graft in relation to the joint, and thus there is avoided friction of the graft against the articular condyles of the femur.

4. The operative procedure is relatively simple.

5. The re-establishing of the normal statics of the knee is accomplished by reversing the angulation through the metaphysis in a direction opposite to that of the acquired deformity and to approximately the same degree.

6. There is no disturbance of or interference with the musculature of the knee.

[ED. NOTE.—I do not believe that Steinmann pins are necessary. Only one Kirschner wire is needed to maintain the upper fragment in hyperextension. If a tongue of bone is left attached to the lower fragment, the second pin is not necessary and one is assured of good bone contact and good apposition of the fragments. One important point that was not brought out is that genu recurvatum does not occur as a single deformity; there is usually some genu valgum and external torsion as well as the recurvatum deformity. All three deformities can be corrected at one procedure if after completing the transverse osteotomy one rotates the distal fragment in such a manner that the external torsion, genu valgum and genu recurvatum are corrected and then with a Gigli saw removes the appropriate wedge of bone from the distal fragment, the sawed surface being parallel with the cut surface of the upper fragment. A description of this procedure can be found in *The Journal of the American Medical Association* for Sept. 26, 1942.]

Mayer,[253] writing on the significance of the iliocostal fascial graft in the treatment of paralytic deformities of the trunk, describes three types, the deformities being classified according to the underlying muscle imbalance. In the first, there is a unilateral paralysis of all the muscles of the trunk. This produces a scoliosis with convexity to the paralyzed side and a downward tilt of the pelvis. This deformity leads to fixed pelvic obliquity. The second is due to the paralysis of external and internal oblique muscles, but the quadratus lumborum muscle remains normal, so that there is no pelvic obliquity. In the third type there is paralysis of abdominal muscles on both sides, producing a downward tilt of the pelvis and an exaggerated lumbar lordosis. He states that these deformities are not always clear-cut but that two of these classifications may be present in one deformity. He stresses the importance of early detection of these deformities followed by early treatment which comprises "well leg traction," pulling down on the elevated side of the pelvis and pushing up on the depressed side. This "well leg traction" may or may not be combined with a Risser type of turnbuckle jacket. He describes in detail the iliocostal fascial transplant which passes from the crest of the ilium to the ninth rib on the same side. Spinal fusion alone is not adequate to control these deformities, because if the muscle imbalance is allowed to remain the scoliosis will promptly recur. Spinal fusion, however, is an important part of the treatment in correcting the three types of deformities he describes with which there is an exaggerated lumbar lordosis. It is not clearcut when a spinal fusion or a fascial graft should be combined. His rule is to do the fascial graft first and observe the patient at three month intervals, and if the scoliosis increases as much as 10 degrees then a spinal fusion should be done. He reports 38 cases in which forty-six grafts were done. The results were good or excellent in 30 cases.

[ED. NOTE.—I cannot conceive of a fixed paralytic pelvic obliquity in the cases described under the first classification, wherein the deformity is confined to the trunk and can be corrected by fascial transplant alone. In these deformities the pelvis is not only oblique but displaced to one side. One must remember that a normal person when taking a step maintains the pelvis in a level position by the abductor muscles pulling down on the weight-bearing side, assisted by the lateral trunk groups pulling up on the opposite side, the femoral head being the fulcrum. When there is a paralysis of the trunk muscles on either side, this balanced system is disrupted. In all these cases there is a severe functional imbalance involving the side below the pelvic level on the side to which it is displaced and diagonally on the opposite side or trunk above the pelvic level. I have always done a Soutter fasciotomy to release the tight hip abductor muscles on the low side of the pelvis, followed by "well leg traction" in the attempt to restore the pelvis to its normal position. Then a fascial transplant is done on the same side. The pelvis cannot be restored to its original position in true fixed pelvis obliquity any more than one can completely correct the scoliosis with rotation. It is surprising how the walking of these persons is improved by simply doing a subtrochanteric osteotomy on the high side of the pelvis and shifting the femur nearer the midline.]

253. Mayer, L.: The Significance of the Iliocostal Fascial Graft in the Treatment of Paralytic Deformities of the Trunk, J. Bone & Joint Surg. **26**:257-271 (April) 1944.

X. POLIOMYELITIS

PREPARED BY J. A. TOOMEY, M.D., CLEVELAND

Paul [254] reports on the localization of the virus of poliomyelitis in human beings and on the epidemiology of the disease.

Howe and Bodian [255] demonstrated virus in a series of 174 specimens of stools from human beings and chimpanzees. They state that if 2 or more test animals were used the recovery rate would be 90 per cent.

Ward and Sabin [256] described 2 patients with poliomyelitis and 1 healthy person from whom poliomyelitis virus had been isolated from the stools in the winter.

Melnick [257] describes rod-shaped particles found with a new electron microscope in the stools of patients with poliomyelitis. They were also present in stools from normal patients; it was impossible to say whether these were the specific virus of poliomyelitis or were normal physiologic constituents of stools. Concrete evidence was lacking.

Howe and Bodian [258] isolated poliomyelitis virus from the stools of 2 uninoculated chimpanzees six months after they were quartered adjoining rhesus monkeys getting intranasal inoculation of potent human stools. They even demonstrated lack of antibody on admission and later development of antibody after isolation of virus from the stools.

Faber [259] and his associates produced poliomyelitis in monkeys (especially cynomologus) with great facility, the route of the infection probably being by the afferent fibers of the fifth cranial nerve. Entry by way of sympathetic fibers of the nose and pharynx was also demonstrated in 1 instance. Faber believes that because of air and dirt contamination this may be a good source of infection.

Rendtorff and Francis [260] found virus in the abdomens of flies; presumably it does not multiply in the gastrointestinal tract. They also recovered it from fecal and vomit spots.

Rinehart [261] believes that there is a predisposing factor in the host which increases his susceptibility to poliomyelitis. He suggests salt depletion and hemoconcentrations as possible factors.

[Ed. Note (J. A. T.).—One wonders why the disease is not more prevalent in the tropics and would agree further that more work needs to be done.]

Rosenow [262] believes that the inciting agent of poliomyelitis represents interrelated phases of the streptococcus and that the virus, as others term it, is the small filtrable invasive nonantigenic phase of the streptococcus.

In another communication, Rosenow [263] reports isolation of a filtrable infectious agent from neurotropic streptococci (the patient had hiccup) which first produced encephalitis and, after successive passages, symptoms and lesions of polioencephalitis in both mice and monkeys. The author believes that this is a "natural" poliomyelitis.

In a subsequent publication, Rosenow [264] brings together all of his experimental work on the filtrable invasive and nonantigenic phase of the streptococcus.

[Ed. Note (J. A. T.).—One can say about all this work only that it does not seem to be accepted by persons working in the field, some of them claiming that they have tried to reproduce Rosenow's experiments, without results, and a few others confirming him. It appears that an unbiased study of this work is indicated.]

254. Paul, J. R.: Poliomyelitis, in Harvey Lectures, 1942-1943, Lancaster, Pa., Science Press, 1943, vol. 38, pp. 104-122.

255. Howe, H. A., and Bodian, D.: Efficiency of Intranasal Inoculation as Means of Recovering Poliomyelitis Virus from Stools, Am. J. Hyg. **40**:224-226 (Sept.) 1944.

256. Ward, R., and Sabin, A. B.: Presence of Poliomyelitis Virus in Human Cases and Carriers During Winter, Yale J. Biol. & Med. **16**:451-459 (May) 1944.

257. Melnick, J. L.: Detection with Electron Microscope of Rod-Shaped Particles in Stools of Normal and Poliomyelitic Individuals, J. Immunol. **48**:25-28 (Jan.) 1944.

258. Howe, H. A., and Bodian, D.: Poliomyelitis by Accidental Contagion in Chimpanzee, J. Exper. Med. **80**:383-390 (Nov.) 1944.

259. Faber, H. K.; Silverberg, R. J., and Dong, L.: Poliomyelitis in Cynomologus Monkey: Infection by Inhalation of Droplet Nuclei and Nasopharyngeal Portal of Entry, with Note on This Mode of Infection in Rhesus, J. Exper. Med. **80**:39-57 (July) 1944.

260. Rendtorff, R. C., and Francis, T., Jr.: Survival of Lansing Strain of Poliomyelitis Virus in Common House-Fly, J. Infect. Dis. **73**:198-205 (Nov.-Dec.) 1943.

261. Rinehart, J. F.: Salt Metabolism in Poliomyelitis, J. Nerv. & Ment. Dis. **99**:825-833 (May) 1944.

262. Rosenow, E. C.: Poliomyelitis: Studies on Inciting Agent and Specific Serum Treatment, Lancet **1**:491-493 (April 15) 1944.

263. Rosenow, E. C.: Production of Filtrable Infectious Agent from Alpha Streptococci, Am. J. Clin. Path. **14**:150-167 (March) 1944.

264. Rosenow, E. C.: Poliomyelitis: Relation of Neurotropic Streptococci to Epidemic and Experimental Poliomyelitis and Poliomyelitis Virus; Diagnostic Serologic Tests and Serum Treatment, Internat. Bull. Econ. M. Research & Pub. Hyg. **A44**:9-83, 1944.

In three papers by Rosenow,[265] the same idea about the Streptococcus is expanded and encephalitis is considered as a kindred entity to poliomyelitis. He calls attention to the fact that only streptococci with neurotrophic properties inherent or induced will yield "neurotrophic" virus. He suggests that the relation between the streptococci and the virus in encephalitis and poliomyelitis is phasal rather than synergistic. In most instances the streptococci were of the alpha type. He describes a cutaneous reaction, a precipitation test, results of agglutination procedures and the other qualities of immunity and antigen sensitivity.

Milzer and colleagues[266] report that the Lansing strain of virus is inactivated in less than one second's exposure to ultraviolet rays and that the inactivated virus could be used as a vaccine to prevent the disease in monkeys and in mice.

[ED. NOTE (J. A. T.).—Before such a vaccine is tried, there is need for more and corroborative evidence.]

Meyer[267] believes that there is an inflammation of the walls of the jugular vein in patients with poliomyelitis, which responds promptly to the application of leeches over the inflamed jugular vein.

[ED. NOTE (J. A. T.).—There is no evidence to support this conception.]

Kramer, Geer and Szobel[268] tested the effects of innumerable agents for their viricidal activity—so far as barbiturates, dyes, organometallic compounds, sulfonamide compounds and a host of chemicals (one hundred and sixty items in all) were employed, with negative results.

[ED. NOTE (J. A. T.).—This is an important and fundamental piece of work.]

Toomey[269] believes that sulfonamide compounds should not be given to patients with poliomyelitis, since experiments show an aggravation of the disease when these drugs are given to experimental animals.

Ehrich and Foster[270] repeated histologic studies of mouse poliomyelitis and found it to be the same as that described by Lillie, Armstrong, Jungeblut and Sanders. There is good correlation between the histologic changes in the central nervous system and the clinical signs.

Jungeblut[271] showed that two strains of human poliomyelitis virus and Theiler's mouse encephalemyelitis virus revealed overlapping in cross neutralization and in antiviral immune serum tests, reciprocal in some but not so in others. He obtained evidence of group specificity after intracerebral tests and of strain specificity after intraperitoneal tests. He believes that all virus previously referred to could be classed under a "poliomyelitis group."

Paul[272] found that grivet and vervet monkeys are more susceptible to poliomyelitis virus than are baboons, and he feels that they are satisfactory animals to work with in experimental poliomyelitis.

Rasmussen and colleagues[273] showed that mice fed an adequate diet save for various levels of riboflavin showed no consistent differences to infection with Theiler's virus. In experiments with the Lansing strain, there was slight but definitely greater resistance in the deficient group.

McCormick[274] has for a long time been of the opinion that thiamine deficiency has something to do with poliomyelitis and that there is an affinity between beriberi and poliomyelitis.

Lichstein and co-workers[275] showed that mice fed rations deficient only in calcium pantothenate have increased resistance to Theiler's encephalitis but the course of the disease following infection with the Lansing virus is not influenced.

265. Rosenow, E. C.: Filterable Infectious Agent Obtained from Alpha Streptococci Isolated in Studies of Case of Poliomyelitis, Am. J. Clin. Path. **14**:519-533 (Oct.) 1944; Specific Streptococcal Antibody-Antigen Reactions in Poliomyelitis: Preliminary Report, Proc. Staff Meet., Mayo Clin. **19**:444-448 (Aug. 23) 1944; Studies on Virus Nature of Infectious Agent Obtained from Four Strains of "Neurotropic" Alpha Streptococci, J. Nerv. & Ment. Dis. **100**:229-262 (Sept.) 1944.

266. Milzer, A.; Oppenheimer, F., and Levinson, S. O.: Production of Potent Inactivated Vaccines with Ultraviolet Irradiation: Abbreviated Preliminary Report on Completely Inactivated Vaccine (Lansing Strain Virus) in Mice, J. A. M. A. **125**:704-705 (July 8) 1944.

267. Meyer, O.: New Principle in Treatment of Poliomyelitis, Internat. Bull. M. Research & Pub. Hyg. **A44-P**:5-9, 1944.

268. Kramer, S. D.; Geer, H. A., and Szobel, D. A.: Chemoprophylactic and Therapeutic Action of Wide Variety of Chemical Compounds on Two Neurotropic Virus Infections in Mice, J. Immunol. **49**:273-314 (Nov.) 1944.

269. Toomey, J. A.: Treatment of Poliomyelitis, J. A. M. A. **126**:49 (Sept. 2) 1944.

270 Ehrich, W. E., and Foster, C.: Experimental Poliomyelitis in Mice: Observations on Its Genesis and on Histologic Changes, Arch. Path. **38**:365-369 (Dec.) 1944.

271. Jungeblut, C. W.: Serologic Relationships Within Poliomyelitis Group of Viruses, Am. J. Pub. Health **34**:259-264 (March) 1944.

272. Paul, J. R.: Susceptibility of East African Monkeys to Experimental Poliomyelitis, Yale J. Biol. & Med. **16**:461-466 (May) 1944.

273. Rasmussen, A. F., Jr.; Waisman, H. A., and Lichstein, H. C.: Influence of Riboflavin on Susceptibility of Mice to Experimental Poliomyelitis, Proc Soc. Exper. Biol. & Med. **57**:92-95 (Oct.) 1944.

(Footnotes continued on next page)

[Ed. Note (J. A. T.).—One wonders about such results when it is learned that the virus was introduced intracerebrally.]

Foster and colleagues [276] enlarge on their theory that a thiamine deficiency protects, and they now show that the protection is not due to a resulting anorexia.

Weaver and colleagues [277] report that the result of their experiments on cotton rats yielded no evidence that avitaminosis D partial inanition and other factors altered the susceptibility of their cotton rats to the Armstrong Lansing strain of poliomyelitis virus. It is felt that their conclusions were justified as regards rats. They mention Toomey's experience with vitamin D–deficient animals.

[Ed. Note (J. A. T.).—It is only fair to point out that Weaver and co-workers used rats, animals which do not acquire rickets from the exclusion of the vitamin D factor but contract the disease only when the calcium-phosphorus ratio is disturbed by an unbalanced diet, a condition which vitamin D alone does not cure. Weaver's work did not repeat Toomey's experiments—experiments in which the virus was introduced by way of the gastrointestinal tract into monkeys, animals susceptible to vitamin D deficiency.]

Toomey and associates [278] were unable to acclimate virus to white rats either overfed or deficient in vitamin B. They confirmed the point raised by Foster and colleagues that there is a difference between vitamin B–deficient animals and overfed or sufficiently fed animals. However, these workers thought that the difference might not be so striking if, despite lack of paralysis, the presence of virus could be demonstrated in the animals that died. When second generation transfers were made with cords of mice that died without paralysis in the first generation, there was no significant difference in the total number of animals paralyzed in the vitamin B–overfed and the vitamin B–deficient groups of animals. These authors suggest that a conclusion the reverse of the usual one could be made, in that in mice overfed with thiamine some slight protection developed and that the development of paralysis in these animals might indicate a slight protection to the virus.

Rasmussen and associates [279] felt that they, as had Foster and co-workers, had proved that mice fed low caloric diets deficient in thiamine showed a lower incidence of infection both to Theiler's and to Lansing's strains of virus. In some thiamine-deficient survivors subsequently given adequate thiamine, paralysis occurred after a prolonged incubation period.

In brief, Foster and colleagues [280] showed that there was more paralysis following injection of Lansing poliomyelitis in mice given more thiamine hydrochloride than in those that had a deficiency.

[Ed. Note (J. A. T.).—Though there was a statistical difference, one wonders whether the statement can be made that deficiency increased resistance.]

Marshall [281] makes an attempt to implicate vitamin C as a factor in the poliomyelitis concept.

[Ed. Note (J. A. T.).—His evidence and authorities quoted do not prove his point.]

Frohring and Toomey [282] showed that in 10 patients with poliomyelitis the biotin content was about 20.6 micrograms, the riboflavin content between 500 and 800 micrograms and the pantothenic acid content between 1,460 and 6,760 micrograms. The biotin and riboflavin contents seemed higher than the figures obtained by other investigators for normal persons.

Wood [283] cites some examples as to how possible reaction might be thrown out of balance

274. McCormick. W. J.: Pathologic Affinities of Beriberi and Poliomyelitis, M. Rec. **157**:414-419 (July) 1944.

275. Lichstein. H. C.; Waisman, H. A.; Elvehjem, C. A., and Clark, P. F.: Influence of Pantothenic Acid Deficiency on Resistance of Mice to Experimental Poliomyelitis, Proc. Soc. Exper. Biol. & Med. **56**:3-5 (May) 1944.

276. Foster, C.; Jones, J. H.; Henle, W., and Dorfman, F.: Comparative Effects of Vitamin B_1 Deficiency and Restriction of Food Intake on Response of Mice to Lansing Strain of Poliomyelitis Virus, as Determined by Paired Feeding Technic, J. Exper. Med. **80**: 257-264 (Oct.) 1944.

277. Weaver, H. M.: Effect of Rachitogenic Diets, Partial Inanition, and Sex on Resistance of Cotton Rats to the Virus of Poliomyelits, J. Pediat. **24**:88-105 (Jan.) 1844.

278. Toomey, J. A.; Frohring, W. O., and Takacs, W. S.: Vitamin B_1 Deficient Animals and Poliomyelitis, Yale J. Biol. & Med. **16**:477-485 (May) 1944.

279. Rasmussen, A. F., Jr.; Waisman, H. A.; Elvehjem, C. A., and Clark, P. F.: Influence of Level of Thiamine Intake on Susceptibility of Mice to Poliomyelitis Virus, J. Infect. Dis. **74**:41-47 (Jan.-Feb.) 1944.

280. Foster, C.; Jones, J. H.; Henle, W., and Dorfman, F.: The Effect of Vitamin B_1 Deficiency and of Restricted Food Intake on the Response of Mice to Lansing Strain of Poliomyelitis Virus, J. Exper. Med. **79**:221-234 (Feb.) 1944.

281. Marshall, R.: Physiological Paralysis Protection, M. Rec. **157**:281-284 (May) 1944.

282. Frohring, W. O., and Toomey, J. A.: Riboflavin, Pantothenic Acid and Biotin Excretion Tests in Patients with Paralytic Poliomyelitis, J. Pediat. **24**: 293-294 (March) 1944.

283. Wood, H. G.: Metabolism of Nervous Tissue in Poliomyelitis, Journal-Lancet **64**:240-242 (July) 1944.

by interference of a virus and thus upset cellular metabolism. The reported interference of poliomyelitis with the anaerobic glycolysis of the brain has not been confirmed.

Nickle and Kabat [284] claim some specific differences in metabolism between brain tissue infected with Western equine encephalomyelitis and that infected with poliomyelitis. Utilization of oxygen of the poliomyelitic brain is below normal with a glucose concentration of 121 mg. per hundred cubic centimeters; with a concentration of 217 mg. per hundred cubic centimeters utilization of oxygen of the encephalitic brain is below normal, but that of the poliomyelitic brain is not. Other substrates were used to show a difference, lactate-glucose, pyruvate-glucose and succinate-glucose.

Gellhorn [285] reports investigations on the influence of muscle pain on muscular incoordination. He concludes that movements are modified in intensity and equality not only by proprioceptive impulses but also by muscle pain.

Kabat and colleagues [286] report a decrease in the lactic acid content of the brains of mice infected with poliomyelitis virus. They feel that this evidence supports the view that the virus may interfere with metabolism.

Carey's publication [287] is fundamental and describes the early histologic changes that occur in the neuromuscular mechanism of experimental poliomyelitis in monkeys. The early loss of the motor end plate was striking. He suggests tentatively that the changes are a result of abnormal excitation of the secretory mechanism of motor end plates which results in progressive exhaustion of the gold-staining axonic substance leading to denervation at the myoneural junction.

Gard [288] describes two colonies of albino mice in which, during epizootics caused by Salmonella enteritidis and Bacillus piliformis, there were 4 and 5 cases of spontaneous mouse poliomyelitis observed. The transfers were easiest when made from the intestine, next easiest from the lymph nodes and then from the tissue of the central nervous system. The involvement of the lymph node was stressed.

Herrarte and Francis [289] described several methods of recovering virus from various biologic specimens.

Bourdillon [290] studied the sedimentation, the electrophonetic mobility and the serologic reactivity of purified Jungeblut's SK adapted mouse strain in its two hundred and seventieth to three hundred and twentieth passage. The injected dose was always 0.03 cc. of serial dilutions.

[Ed. Note (J. A. T.).—The article is a technical one; suffice it to say that it is one not well suited for abstract.]

Foster and Ehrich [291] describe the technics which they used to demonstrate the alterations of brain and spinal cord characterizing infection with Lansing strain of virus in the mouse.

Bourdillon [292] describes in detail the methods of purification of virus by means of the Swedish angle centrifuge.

A long article on the therapy of poliomyelitis in the acute stages of the disease has been written by Toomey.[293] He concludes:

1. As first shown by Feiss, immobilization and splints are unnecessary in the acute stages of poliomyelitis.

2. Active movement, manipulations, etc., in the acute stage of the disease do not harm the patient.

3. Some form of heat should be used to bring about vascular dilatation in the early stages of the disease. The muscles should be moved through their normal arcs.

4. Muscle reeducation plays the most important role in poliomyelitis therapy. It should be started early and should be persistently carried out over a long period of time.

An excellent article by Ward [294] is devoted to the epidemiology of poliomyelitis. He gives a good review of the probable epidemiologic facts known to date.

284. Nickle, M., and Kabat, H.: Specificity in Effects on Brain Metabolism of Two Differing Neurotropic Viruses, J. Exper. Med. **80**:247-255 (Sept.) 1944.

285. Gellhorn, E.: Effect of Muscle Pain on Central Nervous System at Spinal and Cortical Levels, Journal-Lancet **64**:242-245 (July) 1944.

286. Kabat, H.; Erickson, D.; Eklund, C., and Nickle, M.: Decrease in Lactic Acid Content of Brain in Poliomyelitis, Science **98**:589-591 (Dec. 31) 1943.

287. Carey, E. J.: Study on Ameboid Motion and Secretion of Motor End-Plates: Anatomic Effects of Poliomyelitis of Neuromuscular Mechanism in Monkey, Am. J. Path. **20**:961-995 (Sept.) 1944.

288. Gard, S.: Observations Concerning the Pathogenesis and the Epidemiology of Mouse Poliomyelitis, Yale J. Biol. & Med. **16**:467-476 (May) 1944.

289. Herrarte, E., and Francis, T., Jr.: Efforts Toward Selective Extraction of Poliomyelitis Virus, J. Infect. Dis. **73**:206-211 (Nov.-Dec.) 1943.

290. Bourdillon, J.: Purification, Sedimentation, and Serological Reactions of the Murine Strain of SK Poliomyelitis Virus, Arch. Biochem. **3**:285-297 (Feb.) 1944.

291. Foster, C., and Ehrich, W. E.: Demonstration of Lesion Produced by Experimental Poliomyelitis in Central Nervous System of Mouse, Arch. Path. **37**: 264-271 (April) 1944.

292. Bourdillon, J.: Heat Inactivation of Murine Strain of SK Poliomyelitis Virus, Arch. Biochem. **3**: 299-303 (Feb.) 1944.

293. Toomey, J. A.: Observations on Treatment of Infantile Paralysis in Acute Stage (Nathan Lewis Hatfield Lecture), Tr. & Stud., Coll. Physicians, Philadelphia **12**:14-25 (April) 1944.

294. Ward, R.: The Epidemiology of Poliomyelitis, J. Bone & Joint Surg. **26**:829-832 (Oct.) 1944.

XI. POLIOMYELITIS: CONVALESCENT TREATMENT AND RELATED SUBJECTS

PREPARED BY ROBERT L. BENNETT, M.D., WARM SPRINGS, GA.

The following articles concerning the treatment of patients in the convalescent phase of acute anterior poliomyelitis will be divided into five parts:

1. Articles on the natural course of poliomyelitis, when no treatment is given.

2. Articles on the purposes, the technics and the results of the so-called orthodox treatment.

3. Articles on the purposes, the technics and the results of the Kenny method of treatment.

4. Articles on the purposes, the technics and the results of combination forms of treatment.

5. Articles on subjects having a direct bearing on treatment.

The Natural Course of Poliomyelitis.—Sherman [295] reports her observations on a group of 70 unselected patients through the entire course of their acute disease and through the first six months of the convalescent phase. The patients received the same general treatment as that essentially required for any acute febrile condition. They were given absolute rest in bed, with as nearly a normal diet as possible, and were disturbed only for rapid physical examinations. Fifty-three of the patients received convalescent or adult blood serum. Kenny packs, splints or special apparatus were not used. Patients were discharged as soon as convalescent, even though the period of quarantine had not expired. Of the 70 patients, 13 (18.5 per cent) were nonparalytic; 9 (13 per cent) had only bulbar involvement, and the remaining 48 (68.5 per cent) had spinal or bulbospinal involvement. Six patients (8.6 per cent) died. At the end of six months, 38 (54.3 per cent) patients who had demonstrable weakness during the acute phase were not handicapped. Of these, 7 (10 per cent) had no detectable weakness and 31 (44.2 per cent) had functionally insignificant weakness. Six (8.6 per cent) had functionally significant weakness but required no therapy, and 7 (10 per cent) had severe weakness requiring braces or surgical treatment.

Hipps and Crook [296] report on a study of 88 patients observed over a period of two and a half years. These patients were divided into three groups: (1) patients treated by rest, splints and plaster casts early in the course of the disease; (2) patients given physical therapy under water early in the course of the disease, and (3) patients who were given no treatment. In the group in which no treatment was given, there was 31.1 per cent improvement. In the group in which early rest, splints and plaster casts were used, there was 33.8 per cent improvement. In the group in which early physical therapy under water was given, 68.5 per cent improvement was noted.

Orthodox Treatment.— Hipps and Crook [296] in presenting the aforementioned 88 patients give in detail the early type of treatment given the patients brought to the hospital soon after onset of the disease and given treatment under water immediately. This treatment consisted in immersing the patient in a pool supplied by flowing hot salt wells and kept constantly at a temperature of 98.6 F. The child was carried to the pool on a canvas stretcher and supported in the pool by this stretcher. Gentle under water massage was given the muscles unless soreness was too intense. As soon as the soreness began to disappear and the child felt that he could or wanted to try movement, a physical therapeutist assisted him in the arc of motion. Actual muscle reeducation was started as soon as soreness and articular limitation permitted.

Toomey and Kohn [297] report results of treatment of 226 patients during the years 1941 and 1942. They present a program of early care that Toomey has used for many years. They make the statement that patients should not walk unless they walk correctly, that is, synchronously and against gravity without any limp and without any added jerking movement that would denote substitution of muscles. Orthopedic devices should be used to support muscles and coordinate movement when the patient becomes active. They further say that the "percentage of patients who will be referred to orthopedic surgeons in the future will be just about the same as in the past, but the patients will be in a better condition to profit by orthopedic aid."

Key [298] outlines his concept of treatment of infantile paralysis during the acute stage, the stage of tenderness and contracture, the convalescent stage and the chronic stage. His treatment is essentially good supportive care during the acute stage and protection of the

295. Sherman, M. S.: The Natural Course of Poliomyelitis, J. A. M. A. **125**:99-102 (May 13) 1944.

296. Hipps, H. E., and Crook, B. L.: Early Treatment of Infantile Paralysis, Arch. Phys. Therapy **25**: 403-407 (July) 1944.

297. Toomey, J. A., and Kohn, P. M.: Poliomyelitis: Results of Treatment During the Acute Stage of the Disease, Am. J. Dis. Child. **67**:393-399 (May) 1944.

298. Key, J. A.: The Treatment of Infantile Paralysis, J. Missouri M. A. **41**:70-73 (April) 1944.

involved segments by immobilization in splints or casts in a neutral position during the stage of tenderness or contracture. In order to prevent stiffness, the splints and casts are removed once or twice a day and the joints moved passively through as great an arc as can be tolerated by the patient. In the convalescent stage, splints or casts are removed and the patient is encouraged to move about in bed and exercise his limbs in order to loosen up the muscles and joints. Once or twice a day he is placed in a tub of warm water and the paralyzed limbs are exercised. Muscle training preferably is carried out by skilled physical therapeutists, but the mother or a nurse may be taught to carry on the prescribed treatment for a given patient in a satisfactory manner. In the chronic stage, orthopedic apparatus is used to prevent deformities and improve function of paralyzed segments. Key states:

> This is the orthodox treatment and when it is properly carried out approximately 80 per cent of the patients who develop infantile paralysis during an epidemic may be expected to recover to a point at which they are normal or practically normal. About 20 per cent will be crippled permanently to a variable degree, but only about 1 per cent will be crippled so severely that they will become wheel chair cases.

These figures are from three recent epidemics. Key also states that he does not approve of the Kenny method and enumerates sixteen reasons why he does not.

Scott and Rountree [299] report on 46 cases which occurred during the period from March to November 1941. Thirty-nine patients had or contracted paralysis shortly after admission to the hospital. Thomas splints and Bradford frames were used for all patients. At the end of two years, accurate follow-up studies were made on 39 of the 46 patients. There were 3 (7.7 per cent) deaths. Nine patients (23 per cent) made a complete recovery. Twelve (30.7 per cent) were released from treatment, and 15 (38.4 per cent) were still under treatment. Of the 12 released from treatment, 7 were able to walk without appliances, 3 were able to walk with appliances and 2 were unable to walk. Of the 15 still under treatment, 8 were able to walk without appliances and 3 with appliances and 4 were unable to walk. "The results of the treatments used are not encouraging."

Kenny Method of Treatment.—O'Connor [300] gives the history of the Kenny method, outlining the aid given to Kenny by the National Foundation for Infantile Paralysis, Inc.

Kenny [301] presents and answers two questions: first, concerning her concept of the disease, acute anterior poliomyelitis, and, second, concerning the treatment for this concept. As evidence of the value of her treatment over "orthodox treatment," she presents first the report of McCarroll (*J. A. M. A.* **120**:517-519 [Oct. 17] 1942) and contrasts this report with that of Bingham (*J. Bone & Joint Surg.* **25**: 647-650 [July] 1943). Kenny feels that her answers given in the latter article substantiate the claim that her contribution is not a treatment for recognized symptoms but an entirely new concept of the disease itself.

Knapp [302] presents his observations on the symptoms and treatment of poliomyelitis. He makes the statement that "Muscle shortening is a positive entity in infantile paralysis and is an important factor in the final function end-result." He states that "'mental alienation' is probably only a minor factor in infantile paralysis and is probably not psychologic in origin as thought by Miss Kenny." Maximum efficiency of muscle function within the limits imposed on it by denervation is the aim of treatment and the explanation for the good results obtained.

[Ed. Note.—Dr. Knapp in this article presents his own opinion of the symptoms and treatment. It is worth while to read of this treatment and the article of Kenny mentioned. As is well known, Kenny and Knapp have worked together since Kenny's first visit to the United States, in 1940.]

Ghormley and colleagues [303] present a report of the committee for the investigation of the Kenny treatment of poliomyelitis, following a resolution passed by the Section on Orthopedic Surgery of the American Medical Association. This committee visited a total of six cities and sixteen clinics. A total of approximately 740 patients were examined. Approximately 650 of these patients had been treated by the method advocated by Miss Kenny. The report discusses four major points of the concept of the disease and outlines the major points of the Kenny treatment. Each of the points outlined was

299. Scott, E. B., and Rountree, G. R.: A Study of Forty-Six Cases of Poliomyelitis, Kentucky M. J. **42**: 182-184 (June) 1944.

300. O'Connor, B.: The Story of the Kenny Method, Arch. Phys. Therapy **25**:231-234 (April) 1944.

301. Kenny, E.: Kenny Treatment of Poliomyelitis, Proc. Interst. Postgrad. M. A. North America (1942), 1943, pp. 312-316.

302. Knapp, M. E.: Observations on Infantile Paralysis, Journal-Lancet **64**:164-168 (May) 1944.

303. Ghormley, R. K., and others: Evaluation of the Kenny Treatment of Infantile Paralysis, J. A. M. A. **125**:466-469 (June 17) 1944; Evaluation of the Kenny Treatment of Infantile Paralysis, Arch. Phys. Therapy **25**:415-420 (July) 1944.

analyzed and discussed. Outstanding in the final comments of the committee are the following:

1. "Miss Kenny's objection to muscle examination and hence the lack of accurate records is to be condemned."

2. Miss Kenny's statement that under orthodox treatment only 13 per cent of the patients recovered without paralysis while under the Kenny method over 80 per cent recovered is a "deliberate misrepresentation of the facts of treatment by other methods."

3. The Kenny method "does not prevent or even minimize the degree of permanent paralysis."

4. The claim by many of those who have used the Kenny method that all paralytic scoliosis can be prevented is open to question, because several more years must elapse before any final conclusions can be reached with regard to amelioration or prevention of paralytic scoliosis by means of the Kenny method.

5. The committee acknowledges that the wide publicity pertaining to the Kenny method has stimulated the medical profession to reevaluate known methods of treatment of this disease and to treat it more effectively.

Gill [304] presents an interpretation of the Kenny concept and treatment of infantile paralysis. He makes this statement:

> It is evident, therefore, that the Kenny methods of treatment are very similar to the orthodox methods, and in many particulars identical with them in spite of the different terminology employed by Miss Kenny. The statement that the two methods have nothing in common displays an ignorance of the orthodox methods.

In general, Gill points out, what is new in the Kenny methods is not particularly good and what is good is not particularly new.

Ransohoff [305] presents results in 33 cases occurring in the epidemic of 1942 and observed through June 1943. In this series of cases, there were 4 (12.1 per cent) deaths; in 1 case (3.3 per cent) there was no follow-up; 7 patients (21.2 per cent) had severe residual paralysis, and 12 (39.3 per cent) were "completely cured." Thus, 21 patients (63.5 per cent) returned to normal or were without functional handicap. Ransohoff makes the statement that the cost of the Kenny treatment is "tremendous" and is "five times as expensive as the orthodox."

Barnett [306] reports on the treatment of 102 patients during the epidemic in Sonomo County, Calif. There was no note of division of patients according to the various types of poliomyelitis, but the conclusion was made that all but 8 per cent of the patients were eventually functionally normal or nearly so and only 2 per cent were seriously involved. The claim is made that patients were more comfortable after two weeks of the disease and better physically with this type of treatment than patients after three months with the old type of therapy.

Horan [307] outlines the Kenny treatment but gives no results. He makes the statement that the Kenny treatment requires much more work than the orthodox. With the older type of treatment, one nurse could easily care for 5 to 10 patients, but the "Kenny method requires 4 to 5 nurses to look after one patient."

Frankel [308] reports on a year's observation of 6 cases. He makes the statement, "If it [Kenny method] only offers the patients greater comfort than the Orthodox therapy and does no harm, it in worthwhile."

Yount [309] outlines the Kenny method but no results of the treatment are given. She discusses the Kenny concept in detail.

Bohnengel [310] discusses the psychobiologic factors in the care of poliomyelitis in the past and present. He makes the following statement:

> The crux of the whole controversy over the Kenny concept lies in the fact that one group of observers, principally the Minneapolis group, is using psychobiologic methods of observation, experimentation and treatment and therefore brings into view only those phenomena which exist at the psychobiologic level of organismic integration. The other group, using more purely physical methods of study, brings into its field of vision only those phenomena which exist at the anatomic-physiologic level of organismic integration. Both groups tend to lose sight of the fact that the two symptoms may be coexistent not only in the same individual but in the same muscle.

Combined Forms of Treatment.—Boines [311] reports on the use of neostigmine and a modi-

304. Gill, A. B.: The Kenny Concept and Treatment of Infantile Paralysis, J. Bone & Joint Surg. **26**: 87-98 (Jan.) 1944.

305. Ransohoff, N. S.: Experiences with the Kenny Treatment for Acute Poliomyelitis in the Epidemic of 1942, Monmouth and Ocean Counties, New Jersey, J. Bone & Joint Surg. **26**:99-102 (Jan.) 1944.

306. Barnett, E. D.: A Recapitulation on One Polio Siege with Some Notes on Hot Pack Therapy, Hospitals **18**:39-41 (Sept.) 1944.

307. Horan, W. A.: Kenny Treatment of Poliomyelitis, Rhode Island M. J. **27**:16-18 (Jan.) 1944.

308. Frankel, C. J.: The Kenny Treatment for Infantile Paralysis—A Year's Observation of Six Cases, Virginia M. Monthly **71**:79-83 (Feb.) 1944.

309. Yount, F.: New Developments in the Study of Poliomyelitis, Arizona M. J. **1**:61-64 (March-April) 1944.

310. Bohnengel, C.: Psychobiologic Factors in the Kenny Concept of Infantile Paralysis, Arch. Phys. Therapy **25**:350-356 (June) 1944.

311. Boines, G. J.: The Use of Prostigmine and a Modified Kenny Technique in the Treatment of Poliomyelitis, J. Pediat. **25**:414-438 (Nov.) 1944.

fied Kenny technic. Of the 21 cases, there were good to excellent end results in all. The modification of the Kenny technic consisted in the elimination of hot packs and the substitution of neostigmine, usually orally but occasionally parenterally as well. No change was made in the usual methods of muscle reeducation of or in the passive joint movement procedure. He states, "Approximately 75 per cent of patients with poliomyelitis can be adequately cared for at home without special nursing attention with this technique." Boines also urges the extension of this method of therapy especially in chronic cases.

McFarland and colleagues [312] make a preliminary report of a series of 74 selected cases in which neurotripsy was combined with the Kenny treatment. In 25 of these cases neurotripsy was done while the Kenny treatment was being given in the acute stage, and in 49 cases of long-standing residual paresis neurotripsy also was done in combination with the Kenny method. The rationale of neurotripsy is the fact that in regrowth after nerve interruption there is an increased branching. The authors present an outline of the procedure, which is done with general or spinal anesthesia with the objective of breaking as many branches of the remaining live motor nerve axons as possible. The technic is to knead through the muscle vigorously and deeply with a blunt instrument. The muscle is covered thoroughly throughout its entire extent. There has been a rather consistent increase in circulation in the involved segments, and an increase in muscle size is a "frequent result." Improvement in muscle strength occurred in over one half of one hundred and thirty muscle groups studied. "The results are encouraging."

Miley [313] presents a preliminary report on 58 cases in which the Knott technic of ultraviolet irradiation of blood was used in addition to the Kenny treatment. There were no harmful effects in this series of cases. This technic did not interfere with the Kenny routines. No attempt was made to evaluate the ultimate end results for these patients, but it is Miley's conclusion that further extensive clinical studies with this combination of treatments is warranted.

Nelson [314] discusses the present status of poliomyelitis. Regarding treatment, he says that hot packs during the stage of spasm followed by muscle reeducation offer the most help in the acute stages.

Compere [315] outlines the management and care of patients with infantile paralysis. He states that his own observation led to the conclusion that the earlier the program of treatment of peripheral manifestations is done the better are the end results. Microscopic sections of muscles that are in spasm show a picture of pathologic congestion. This congestion may be relieved by hot packs, passive motion and active exercise. He further concludes that the number of patients who will require surgical intervention may be as large as that of the patients who have received other types of treatment but that the patients given treatment by hot packing, early activity, exercises and good physical therapy will be in better condition generally and will thus obtain greater profit from the efforts of the orthopedic surgeon.

Wright [316] presents problems encountered in the early treatment of poliomyelitis. She states that Kenny has made a valuable contribution but that one will continue to use to advantage the Silver method of the prevention of stasis of the circulation by special postural measures in bed, the Lovett-Merrill method of muscle testing, the Kendall percentage grading, the Lowman under water reeducation and the light, efficient supports when indicated. In a second article, Wright [317] outlines a reasonable program of treatment for acute poliomyelitis. She notes that "treatment can not be by one method only but must meet the needs of each case."

Wolf,[318] in discussing the clinical aspects of poliomyelitis, states that "when a patient with pure bulbar poliomyelitis is placed in a respirator it can be seen that more harm than good results. The patient breathes with the machine at times and against it at others. The use of the respirator under these conditions may be extremely harmful."

Thompson [319] discusses the Kenny method and correlates a program of occupational therapy combined with the Kenny method.

312. McFarland, J. W.; Billig, H. E., Jr.; Taylor, G. M., and Dail, C. W.: Kenny Treatment Combined with Neurotripsy in Care of Poliomyelitis, Arch. Phys. Therapy **25**:645-650 (Nov.) 1944.

313. Miley, G.: Ultraviolet Blood Irradiation Therapy in Acute Poliomyelitis, Arch. Phys. Therapy **25**: 651-656 (Nov.) 1944.

314. Nelson, N. B.: Poliomyelitis: Its Present Status, California & West. Med. **60**:18-21 (Jan.) 1944.

315. Compere, E. L.: Management and Care of the Infantile Paralysis Patient, Arch. Phys. Therapy **24**: 709-712 (Dec.) 1943.

316. Wright, J.: Problems in Early Treatment of Poliomyelitis, New York State J. Med. **44**:67-72 (Jan. 1) 1944.

317. Wright, J.: Reasonable Treatment of Acute Poliomyelitis, Pub. Health Nursing **36**:510-515 (Oct.) 1944.

318. Wolf, A. M.: Symposium on the Management of Poliomyelitis, Am. J. Dis. Child. **67**:332-334 (April) 1944.

(Footnotes continued on next page)

Additional Reports Bearing on Treatment.—Kabat and Knapp [320] present the "internuncial cell theory" of the mechanism of muscle spasm. They discuss muscle spasm in detail and present evidence to support the theory that the pathologic basis of muscle spasm in poliomyelitis is a lesion of internuncial neurons in the gray matter of the spinal cord. With damage to these cells, the muscle spasm is produced as a result of the release of proprioceptive reflexes from inhibition. They support this theory by animal experimentation, by the study of pathologic changes in the spinal cord in 68 cases of poliomyelitis in human beings, by measurement of chronaxia of muscles in 14 patients and by the use of neostigmine acting on the spinal cord to inhibit proprioceptive reflexes.

Bouman and Schwartz [321] discuss muscle spasm and demonstrate its existence by means of action currents. They state that the motor neuron receives three separate groups of impulses: (1) impulses which give rise to voluntary contraction; (2) inhibitory impulses, and (3) excitatory impulses from the reflex arcs. They feel that if only the excitability to inhibitory impulses is gone the motor unit innervated by the particular neuron will show spasticity but no decrease in voluntary function. If both the inhibitory and the voluntary impulses are no longer able to excite the motor neuron, spasticity will be present, while the muscles will show decreased function, and, finally, when all motor neurons have lost the excitability to all three types of impulses both voluntary contraction and spasticity of muscles will disappear.

Schwartz and colleagues [322] present the etiology, pathogenesis and significance of muscle spasm in acute poliomyelitis, to bring out the fact that evidence of spasticity has been recorded from (*a*) weakened muscles; (*b*) antagonists of weakened muscles, and (*c*) muscles which exhibit no clinical or other evidence of weakness. They feel that spasticity and weakening are two separate phenomena, each dependent on specific disturbances of the anterior horn cells. They further feel that there is every indication that spasm runs its course like other clinical manifestations of the disease.

Moldaver,[323] in an analysis of the neuromuscular disorders in poliomyelitis, brings out the fact that paralytic and paretic muscles, called "alienated" under the Kenny concept of the disease, always show some degree of neuromuscular degeneration. The extent of this degeneration can be shown by chronaxia determinations. It is his opinion that there are three major causes of spasm: (1) meningeal irritation; (2) shortening of uninvolved antagonistic muscles, and (3) inflammation of the posterior root ganglions.

McFarland and Graves [324] outline a method of recording muscle spasm in the acute stage of infantile paralysis and the degree of tightness or contracture present in the convalescent stage.

Gurewitsch and O'Neill [325] analyze a group of 513 children between the ages of 4 and 18 years. These children were given five simple flexibility tests. The performances were found to vary widely. The authors emphasize that constitution, heredity and sex are factors in normal flexibility, and they suggest that caution be used in the interpretation of limited flexibility encountered in patients during convalescent stages of poliomyelitis.

Hall and colleagues [326] state that hot packs applied to muscles temporarily decrease the power of voluntary contraction about 10 per cent.

Stevenson [327] discusses the problem of public health nursing as it was demonstrated in the 1943 epidemic of poliomyelitis.

Draper [328] presents a statewide emergency plan to care for an epidemic of poliomyelitis. This plan includes an educational program stressing the need for early care and the essential teamwork of physician, nurse and physical therapy technician. She presents a preliminary report of results obtained in 87 cases under this plan. Fifty per cent of the patients returned to normal

319. Thompson, C. G.: Occupational Therapy and the Kenny Method, Occup. Therapy **22**:270-273 (Dec.) 1943.

320. Kabat, H., and Knapp, M. E.: The Mechanism of Muscle Spasm in Poliomyelitis, J. Pediat. **24**:123-137 (Feb.) 1944.

321. Bouman, H. D., and Schwartz, R. P.: The Degree, the Extent and the Mechanism of Muscle Spasm in Infantile Paralysis, New York State J. Med. **44**:147-153 (Jan. 15) 1944.

322. Schwartz, R. P.; Bouman, H. D., and Smith, W. K.: The Significance of Muscle Spasm, J. A. M. A. **126**:695-702 (Nov. 11) 1944.

323. Moldaver, J.: Analysis of Neuromuscular Disorders in Poliomyelitis, J. Bone & Joint Surg. **26**:102-117 (Jan.) 1944.

324. McFarland, J. W., and Graves, D. A.: Poliomyelitis: Grading of Spasm in Infantile Paralysis, Arch. Phys. Therapy **25**: 553-556 (Sept.) 1944.

325. Gurewitsch, A. D., and O'Neill, M. A.: Flexibility of Healthy Children, Arch. Phys. Therapy **25**: 216-221 (April) 1944.

326. Hall, V. E.; Schamp, H. M.; Brown, C. E., and Davis, M. N.: Effect of Kenny Fomentation on the Strength of Voluntary Muscular Contracture in Man, Arch. Phys. Therapy **25**:96-99 (Feb.) 1944.

327. Stevenson, J. L.: Public Health Nursing in the 1943 Polio Epidemic, Pub. Health Nursing **36**:336-339 (July) 1944.

328. Draper, E.: An Emergency Plan in High Incidence Poliomyelitis, Physiotherapy Rev. **24**:96-99 (May-June) 1944.

occupation; 14 per cent obtained good results but have not yet returned to normal activity; 14 per cent obtained fair results, with no complete paralysis but with definite weakness, and 22 per cent had a residual definite loss of one or more muscle groups.

Poehler [329] outlines an ideal set-up for the treatment of poliomyelitis following the remodeling of "Sheltering Arms" in Minneapolis. She stresses the fact that patients during the convalescent stage of poliomyelitis are not sick in the sense that the word is usually understood and should not be treated in hospitals planned and maintained for acutely ill persons.

Gudakunst [330] discusses the problem of infantile paralysis, setting forth the gains made in the handling and treatment of patients. He brings out the purpose and scope of the work of The National Foundation for Infantile Paralysis, Inc.

329. Poehler, J. A.: Remodeled for "Polio" Patients, Mod. Hosp. **62**:58-60 (Jan.) 1944.

330. Gudakunst, D. W.: Fighting Infantile Paralysis, Survey **80**:254-256 (Sept.) 1944; Facing the Future in the Fight Against Infantile Paralysis, J. Health & Phys. Educ. **15**: 258 (May) 1944.

XII. NEUROMUSCULAR DISORDERS EXCLUSIVE OF POLIOMYELITIS

PREPARED BY WINTHROP M. PHELPS, M.D., BALTIMORE

During 1943 there was an increase in the volume of literature dealing with neuromuscular disorders. This is especially interesting in view of the pronounced decrease of the year before. The distribution of the material has changed only slightly. That referring to cerebral palsy has increased the most, and the articles on peripheral paralysis and surgery are close seconds. The papers dealing with pure research in the field are still scarce.

The material can be considered under nine chief headings, which are as follows: (1) cerebral palsy, (2) peripheral paralysis, (3) myopathies, (4) ataxia, (5) neuralgia, (6) diagnostic procedures, (7) surgery, (8) vitamins and (9) drugs.

Cerebral Palsy.—A paper by Lucksch [331] describes 2 cases, brought to autopsy, of the disease previously called "cerebral infantile paralysis." Lucksch suggests that the designation be changed to "encephalopathia infantum." The change, he feels, is more descriptive of conditions observed and yet is not specifically a description of a disease entity. [ED. NOTE.—This is an anatomic title whereas the usual term "cerebral palsy" is a descriptive one, and the latter, of course, is much more in keeping with American custom.]

Yannet [332] has written an interesting paper on the study of 86 patients with cerebral palsy. He notes that the average age of the mother at the time of birth of the affected child is greater than that found in the general population. The affected children tend to have a later ordinal birth rank than would be normally expected. [ED. NOTE.—This might be expected in view of the recent observations in regard to the Rh factor.] He also finds that the incidence of mental deficiency in the nonaffected siblings is greater than would be expected from random selection. He finds an unusually high incidence of associated physical defects, especially those involving the eyes. [ED. NOTE.—In my experience, this is also true of hearing defects.] Yannet feels that this points to the importance of developmental cerebral malformations in the causation of cerebral palsy.

Phelps [333] describes the treatment of various types of cerebral palsy in some detail and emphasizes the need for proper classification of the individual cases in order to carry out differential treatment.

Salisbury [334] draws attention to the increased interest in cerebral palsy throughout the country and the greater number of cases encountered in the clinics and in private practice and emphasizes the great need for a national foundation for this condition, since it is as frequent in distribution as poliomyelitis.

Arieff and Kaplan [335] describe cerebellar ataxia associated with cerebral signs. This is, of course, not commonly seen, but it is well to bear in mind the complications of neurologic changes which may occur.

Welch and Kennard [336] describe flaccid paralysis in relation to the cerebral cortex. This is

331. Lucksch, F.: Description of Two Autopsy Cases of "Cerebral Infantile Paralysis," with Suggestion for Changing Designation to "Encephalopathia Infantum," Psychiat.-neurol. Wchnschr. **45**:137 (May 22) 1943.

332. Yannet, H.: Etiology of Congenital Palsy: Statistical and Clinical Study, J. Pediat. **24**:38-45 (Jan.) 1944.

333. Phelps, W. M.: Symposium on Orthopaedic Surgery: Treatment of Cerebral Palsies, Clinics **2**:981-991 (Dec.) 1943.

334. Salisbury, P. A.: Needed—National Foundation for Cerebral Palsy, Hospitals **18**:50-53 (April) 1944.

335. Arieff, A. J., and Kaplan, L. A.: Cerebellar Type of Ataxia Associated with Cerebral Signs, J. Nerv. & Ment. Dis. **100**:135-141 (Aug.) 1944.

(Footnotes continued on next page)

important and was described some years ago by other investigators, in both the experimental and the clinical fields. The combination of spastic and flaccid paralysis does occur in many instances and is of cortical origin.

Thiébaut [337] describes spastic paralysis associated with xanthomas of tendons and describes the relationship of this syndrome to cerebrospinal cholesterinosis. The cerebral changes are important to bear in mind in any cases of xanthoma.

A number of articles have appeared this year on various types of treatment of the cerebral palsies.

Sidler [338] speaks of the general plan of therapy for children and goes into some detail with regard to methods.

Frank [339] writes concerning the advantages and the usefulness of occupational therapy for children with cerebral palsy, and Mason [340] describes speech rehabilitation in such cases.

Teza [341] writes concerning the motor reeducation in these cases as it is being carried out in Argentina.

Peripheral Paralysis.—Chavany [342] describes a post-traumatic neurologic syndrome with increasing atrophy and fibrillary contractions, which is of interest because of its traumatic origin.

Denny-Brown and Brenner [343] discuss paralysis produced by pressure and tourniquets in an article on the subject, with much more careful experimentation. They conclude that there is great variation of the rate of impairment of induction with variations in pressure and that the relationship is an expression of corresponding relative degrees of ischemia and not direct consequence of pressure on nerve fibers. They describe in detail the microscopic histologic changes which occur by various staining methods. They conclude that from the evidence presented atrophy of a paralyzed muscle appears to be prevented by anatomic connection with the motor neuron in the absence of nerve impulses.

Dunning [344] reports a case of injury to the peroneal nerve (with foot drop) due to crossing the legs and points out that this habit may cause injury to the nerve. [ED. NOTE.—It does not seem as if the danger is especially great unless there is some other complication in the blood or the nerve supply, since this practice is certainly almost universal.]

Lewin [345] and Laird and Mueller [346] also consider peroneal paralysis but from different causes. The former considers that it is a definite pressure palsy (of the lateral popliteal nerve) in the paralyzed limb, while the latter authors describe it as a "bombardier's palsy."

Connell [347] describes a case of paralysis which appears to have resulted from the use of dinitrotoluene. The patient was treated by rest in bed and made a gradual partial recovery. The author cites other cases of the same type which have been observed and which resulted in death.

MacKeith [348] describes paralysis of the extremities due to polyarthritis nodosa and Love and Horton [349] an ulnar paralysis due to arteriovenous fistula.

Myopathies.—Laha [350] considers the question of myatonia congenita (a subject on which little has been written in the last few years).

Shank, Gilder and Hoagland [351] review 40 cases of progressive dystrophy with regard to the changes that occur in various stages of the disease and the age distribution and the onset.

336. Welch, W. K., and Kennard, M. A.: Relation of Cerebral Cortex to Spasticity and Flaccidity, J. Neurophysiol. **7**:255-268 (Sept.) 1944.

337. Thiébaut, F.: Spastic Paraplegia Associated with Xanthomas of Tendons: Relation of This Syndrome to Cerebrospinal Cholesterinosis, Rev. neurol. **74**:313-315 (Nov.-Dec.) 1942.

338. Sidler, A.: Therapy of Spastic Paralysis in Children, Praxis **33**:261-264 (April 20) 1944.

339. Frank, C.: Occupational Therapy for Children with Cerebral Palsy, Occup. Therapy **23**:103-114 (June) 1944.

340. Mason, M. K.: Speech Rehabilitation, Physiotherapy Rev. **23**:237-242 (Nov.-Dec.) 1943.

341. Teza, A.: Kinesitherapy of Little's Disease: Motor Education, Arch. argent. de pediat. **21**:181-186 (Feb.) 1944.

342. Chavany, J. A.: Post-Traumatic Neurologic Syndrome: Extensively Progressive Amyotrophy with Secondary Paralysis and Fibrillary Contractions, Presse méd. **50**:347 (May 10) 1942.

343. Denny-Brown, D., and Brenner, C.: Paralysis of Nerve Induced by Direct Pressure and by Tourniquet, Arch. Neurol. & Psychiat. **51**:1-26 (Jan.) 1944.

344. Dunning, H. S.: Injury to Peroneal Nerve (with Foot Drop) Due to Crossing the Legs, Arch. Neurol. & Psychiat. **51**:179-181 (Feb.) 1944.

345. Lewin, W.: Pressure Palsy (of Lateral Popliteal Nerve) in Paralyzed Limb, Lancet **2**:756-758 (Dec. 18) 1943.

346. Laird, G. J., and Mueller, M. J.: Bombardier's Palsy, Air Surgeon's Bull. (no. 9) **1**:19 (Sept.) 1944.

347. Connell, E. D.: Paralysis from Chemical Poisoning (Probably Dinitrotoluene): Case, Memphis M. J. **19**:59-60 (April) 1944.

348. MacKeith, R.: Localized Subcutaneous Edema with Weakness of Limb Muscles: Syndrome Due to Polyarthritis Nodosa, Brit. M. J. **1**:139-142 (Jan. 29) 1944.

349. Love, J. G., and Horton, B. T.: Paralysis of Ulnar Nerve Due to Arteriovenous Fistula, Proc. Staff Meet., Mayo Clin. **19**:441-444 (Aug. 23) 1944.

350. Laha, P. N.: Amyotonia Congenita, with Illustrative Case Note, J. Indian M. A. **13**:20-22 (Oct.) 1943.

351. Shank, R. E.; Gilder, H., and Hoagland, C. L.: Progressive Dystrophy: Clinical Review of Forty Cases, Arch. Neurol. & Psychiat. **52**:431-442 (Dec.) 1944.

They discuss the previous methods of treatment, including amino acids, vitamins, glandular preparations and other agents. They report extensive studies of basal metabolic rates, tolerance tests, and other aspects of the disease. Their study of the distribution shows the definite hereditary nature of the condition.

Mackay [352] presents an interesting case of dystrophy and the status of treatment at the present time. The particular type which he describes is the Charcot-Marie-Tooth type.

Schwartz [353] also describes the various effects of progressive neuropathic (peroneal) muscular atrophy (Charcot-Marie-Tooth disease), pointing out the inheritance factors as well as the clinical observations.

Ataxia.—Brugsch and Hauptmann [354] describe an interesting combination of Friedreich's ataxia in combination with neuropathic (peroneal) muscular atrophy (Charcot-Marie-Tooth disease).

Neuralgia.—Doupe, Cullen and Chance [355] discuss the causalgic type of pain that is found in post-traumatic neuralgia.

Diagnostic Procedures.—There has been considerable work done in electromyographic study on the various forms of nerve-muscle disturbances in the last few years.

Brazier, Watkins and Schwab [356] illustrate the difference in various types of polyneuritis and poliomyelitis with regard to electromyographic records.

Hoefer and Guttman [357] have made extensive electromyographic studies to determine the level of spinal cord lesions. They present the results in 24 cases and conclude that motor unit discharges recorded from the relaxed muscles may indicate the level of a lesion of the spinal cord, even in the absence of clinical manifestations suggestive of involvement of the anterior horn cells or motor roots. In 17 of 24 cases the lesion was satisfactorily localized, and in the others fairly close localization was obtained; false localization was obtained in only 2 cases.

De Jong [358] has devised an instrument for electrical examination and treatment of peripheral nerves, which is a small light unit and accomplishes many purposes by virtue of features usually not combined in a single instrument.

Pollock and others [359] have studied denervated muscles with various amperages of current and noted the changes which occur when regeneration is taking place.

Licht [360] has formulated an outline of electrodiagnosis of neuromuscular disease for the army.

Surgery.—Cerebral Palsy: Chandler [361] described the surgical procedures which are in present use for correcting deformities of spastic paralysis and the indications for and the various results obtained by the different operations.

Peripheral Nerve: Schulze [362] has described a method of operation for correcting the deformities due to paralysis of the trapezius muscle.

Huguier and Nardi [363] have corrected the paralysis of the arm due to stretching of the brachial plexus by an injury. They have carried out this by a combination of arthrodesis of the shoulder and wrist and transplantation of the tendon. The results have been satisfactory function in the arm for considerable usefulness.

Weiss [364] has devised technics for the union of severed nerves without sutures, by the use of tantalum cuffs.

352. Mackay, R. P.: Progressive Muscular Dystrophy, Proc. Interst. Postgrad. M. A. North America (1943), 1944, pp. 88-91.

353. Schwartz, L. A.: Clinical, Histopathologic and Inheritance Factors in Peroneal Muscular Atrophy (Charcot-Marie-Tooth Type), J. Michigan M. Soc. **43**: 219-230 (March) 1944.

354. Brugsch, H. G., and Hauptmann, A.: Familial Occurrence of Friedreich's Ataxia with Charcot-Marie-Tooth Neural Muscular Atrophy, Bull. New England M. Center **6**:42-48 (Feb.) 1944.

355. Doupe, J.; Cullen, C. H., and Chance, G. Q.; Post-Traumatic Pain and Causalgic Syndrome, J. Neurol., Neurosurg. & Psychiat. **7**:33-48 (Jan.-April) 1944.

356. Brazier, M. A. B.; Watkins, A. L., and Schwab, R. S.: Electromyographic Studies of Muscle Dysfunction in Infectious Polyneuritis and Poliomyelitis, New England J. Med. **230**:185-189 (Feb. 17) 1944.

357. Hoefer, P. F. A., and Guttman, S. A.: Electromyography as Method for Determination of Level of Lesions in Spinal Cord, Arch. Neurol. & Psychiat. **51**: 415-422 (May) 1944.

358. de Jong, H.: Simplification of Method of Electrical Examination and Therapy of Nerves and Muscles, North Carolina M. J. **5**:91-92 (March) 1944.

359. Pollock, L. J., and others: Electrodiagnosis by Means of Progressive Currents of Long Duration: Studies on Cats with Experimentally Produced Section of Sciatic Nerves, Arch. Neurol. & Psychiat. **51**:147-154 (Feb.) 1944.

360. Licht, S.: Neuromuscular Electrodiagnosis: Outline, Bull. U. S. Army M. Dept., January 1944, no. 72, pp. 74-80.

361. Chandler, F. A.: Surgical Procedures Commonly Used in Correcting Deformities of Spastic Paralysis, Clinics **2**:992-1001 (Dec.) 1943.

362. Schulze, R.: Trapezius Paralysis; Surgical Therapy, Zentralbl. f. Chir. **70**:692 (May 8) 1943.

363. Huguier, J., and Nardi: Complete Impotence of Arm Due to Traumatic Elongation of Brachial Plexus: Arthrodesis of Shoulder and of Wrist with Tendon Transplants; Satisfactory Functional Result, Mém. Acad. de chir. **68**:168-173 (Feb. 11-March 4) 1942.

364. Weiss, P.: Sutureless Reunion of Severed Nerves with Elastic Cuffs of Tantalum, J. Neurosurg. **1**:219-225 (May) 1944; Technology of Regeneration: Review; Sutureless Tubulation and Related Methods of Nerve Repair, ibid. **1**:400-450 (Nov.) 1944.

Young [365] points out the advisability of as early suturing as possible and the effects of delay.

Thomsen [366] and Thomsen, Altamirano and Luco [367] have discussed the effects of tenotomy on muscle contractures and neuromuscular transmission.

Blalock [368] reports favorable results in the treatment of myasthenia gravis by thymectomy.

Vitamins.—The work with vitamins has become less and less significant in the last two years with regard to their effects on neuromotor pathologic changes in general. There are, of course, exceptions to this, but these changes occur apparently only in the presence of severe avitaminosis, and it appears that relative avitaminosis is not of so much importance.

Hines, Lazere and Thomson [369] described the effects of different intakes of vitamins of the B complex on neuromuscular regeneration and found that it was not affected by withdrawal of the vitamins and that excess intakes caused no enhancement of regeneration.

Hines, Lazere and Thomson [370] discuss a similar study with regard to the effects of vitamin C on neuromuscular regeneration in guinea pigs. They conclude that the regenerating muscles of animals subsisting on low intakes of ascorbic acid were weaker than those with a sufficient quantity but that excess intakes of ascorbic acid had no beneficial effect.

Minot and Frank [371] confirmed previous writers in the fact that vitamin E therapy is not noticeably effective against pseudohypertrophy.

Mims [372] discusses the same question for the myopathies, with a conclusion that there is little if any value in use of vitamin E for these conditions.

Drugs.—The use of drugs for neuromotor conditions has increased considerably in the last year or two, and articles about their use are beginning to appear with greater frequency. The effects of curare and its synthetic derivatives are being widely tested, but as yet few articles concerning this have appeared in the literature.

Chiodin [373] describes the effect of curare and erysopine in the treatment of spastic paralysis, with some evidence of improvement in certain of these conditions.

Schaubel [374] discusses neostigmine as an adjunct in the treatment of cerebral palsy and notes definite improvement in some of the patients, especially in the field of their speech.

Oppikofer [375] discusses the use of neostigmine in treatment of myasthenia gravis and points out the effectiveness of this drug.

Hoagland, Shank and Gilder [376] discuss the effect of testosterone propionate on creatinuria in progressive atrophy and dystrophy. They feel that if excretion of creatinine which occurs after testosterone medication may be regarded as a true storage phenomenon, it would justify the administration of this hormone over a prolonged period to see whether muscle function could be improved thereby. Their report is a preliminary one at the present time.

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